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ROLE OF THE CLINICIAN IN MODERN DERMATOLOGY

President's Address

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TONIGHT I have no scientific contribution, no announcement of a startling invention and no statistical study. We are living in an age when epoch-making discoveries crowd one another from the stage of life in rapid succession. Before we can fully evaluate the effect of one upheaval on the state of our established knowledge we must direct our thinking into another channel to adjust ourselves to something new again. Such continuous adaptation in the field of medicine, difficult though it is, may be accomplished by a mature and experienced mind. To a young physician who is still mastering the alphabet of medical thinking it must be so disturbing, however, as to make difficult the establishment of a permanent base. The great speed of our journey in the quest of knowledge makes it imperative that we stop looking forward occasionally, survey our present and direct our eyes backward to see where we have been. Let us make such a pause tonight.

The remarks I have to make will be addressed chiefly to the younger dermatologists and to the embryos in our midst. For my contemporaries and my elders I have only words of gratitude. In our specialty, probably more than in others, a man does not rise by his own efforts alone. He cannot by himself learn dermatology from books or from pictures or even from patients. He must be taught, he must be guided, and his errors must be corrected. To my colleagues I am indebted for opportunities given me for work and study, for their vast knowledge and experience which they have made available by the presentation and discussion of cases before this society and especially for their help in calling to my attention mistakes which I have made in patients who have left me. All too often we assume smugly that patients who do not return to us have been given correct diagnosis and treatment and are well. It is of great service to be informed when we are wrong. A mistake repeated a hundred times is not instructive, and it cannot be tabulated as experience. An error made once, however, and corrected promptly has educational value. It is a tribute to the genuine friendship and intellectual maturity that exist among the dermatologists of

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our community that we inform one another of errors made and of further developments in our transferred private patients just as we do in the clinic. In thanking my colleagues for such help given me I believe that I am speaking for you all, for in this sphere of mutual education we are all dependent on one another.

In the course of my work in our specialty I have become aware of many thoughts stimulated by my experience with patients and with other dermatologists. These random thoughts have accumulated over the years and have gradually arranged themselves into a definite pattern. Undoubtedly this pattern, or philosophy, that each of us develops on the basis of his own experience becomes the determining influence in his approach to the medical problems that confront him. I am certain that the thoughts which I have accumulated I own in common with most dermatologists. In giving them voice, therefore, I feel that I am speaking for many of you, especially when I discuss the role of the clinician in modern dermatology.

In these days of great scientific advances in medicine, the term clinician has come to carry with it the stigma of negativity. When a physician's obituary notice is being written and there are no scientific accomplishments that can be credited to his life, when he has written nothing of importance and has taught no one, there is always the modest statement that he was a good clinician. The term seems to carry with it the somewhat contemptuous connotation that, in the absence of other medical virtues, the physician had patients and they somehow got along well. Actually, in correct usage, the term clinician is one deserving of honor. It denotes a physician who studies diseases at the bedside or in actual contact with the patient. The great clinicians are those whose studies of disease are directed into channels of constructive investigation by the stern discipline of having as their taskmaster a person who is sick. A clinician does not merely practice the art of amelioration of symptoms. He is a painstaking searcher for all the physical signs and symptoms that may point to an eventual diagnosis. He must be familiar with all forms of laboratory investigation that may add significant clues. Above all he is a physician treating a patient, and he must evaluate wisely the entire case before him.

Most of the dermatologists of previous generations received their primary training in our specialty by acting as assistants to older dermatologists. During such apprenticeship, which in many cases was extended into permanent association, the students were able to observe at close range the methods of study and work that their preceptors had developed through years of experience. Often the philosophies and methods of practice had been handed down through several generations of dermatologists with extensive development by each, and the apprentices were benefiting by close contact with a great heritage. If the preceptors were themselves well versed in pathology, mycology, bac-

teriology or other laboratory fields, the apprentices, too, pursued training in those directions. But above all else they became good clinicians.

Today opportunities for such training are comparatively few. The number of physicians seeking to enter our specialty has increased tremendously, and it is impossible to provide an adequate preceptor for each potential apprentice. Furthermore, the laboratory aspects of dermatology have been developed so intensively and so far that few men are qualified by experience or facilities to teach them all. It has become necessary, therefore, to establish courses of instruction for larger groups in which students receive training in many branches of dermatology from teachers who are especially well qualified in those fields. Some of these teachers are practicing dermatologists; others, especially in the basic sciences, are strictly laboratory men. An attempt is always made to correlate all of the teaching, so that in the course of training students will dovetail all that they have learned into compact and well rounded-out patterns and will emerge fully prepared to stand on their own feet as practicing dermatologists. Are such concentrated departmentalized courses succeeding in this aim? In their contact with patients dermatologists stand or fall on their qualifications as good clinicians and on no other basis. Can any course of formal training by itself succeed in turning out dermatologists who are fully equipped for practice? It is unfortunate that in all formal teaching the emphasis is generally placed on the definite and dogmatic. It is much easier to help students to recognize, let us say, elastic fibers under the microscope, a culture of Microsporon lanosum or the blood picture in lymphatic leukemia than it is to transmit to them the composite of all impressions that we call clinical judgment. And yet this intangible clinical judgment must be possessed by every dermatologist before it is safe for him to establish his own office where he is alone with his patient and his conscience. Clinical judgment is not an inborn characteristic; it is always developed. It is the composite of keen observation, controlled experience and sound reasoning. In our time the powers of observation are being dulled by the plethora of gadgets at our command. We have the equipment and laboratory procedures to take our patients apart down to the very elements that compose them. We can analyze them physically and emotionally. We can even plot graphs to determine the course of their disease by barometric pressures.

It is a wholesome and a humbling experience to look back across the years to the men who did so much to advance the early knowledge of dermatology, who worked long before the advent of our many mechanical aids and who merely observed and reasoned. Among the interesting works of the old masters, there is nothing more fascinating than the writings of Ferdinand Hebra, whose treatise, "On Diseases of the Skin," was published between 1866 and 1880. It is remarkable

how much this great clinician was able to recognize and describe by the mere use of his powers of observation. More amazing is the tremendous amount of his teaching that is still valid in spite of the continuous attacks of time and progress against its stability. Hebra's description of psoriasis leaves little to be added even today. In discussing the treatment of psoriasis he included most of the internal and local medications that we still find useful, and he appraised them with a wisdom that would be enviable even in our advanced time. In introducing the section on the treatment of psoriasis, for example, he stated [1]:

> For the cure of psoriasis, and indeed of chronic diseases of the skin generally, two methods have from early times been proposed. The first of these started from the supposition that all the chronic dermatoses are children of one parent, the products of one and the same dyscrasia or morbid change in the blood; and, therefore, that these diseases are to be cured by purifying and correcting the state of the circulating fluid, or by expelling acrid matters. For the practice of this mode of treatment, no accurate diagnosis was required. . . . The unsatisfactory results yielded by this plan led physicians to enter upon an entirely different path, that of experiment and observation. Now this path is, I must confess, the one which I myself follow exclusively in the treatment of cutaneous affections and indeed of disease in general. I set not the slightest value on any remedies except those which (after repeated trials and when I am accurately acquainted with the complaint) I find to produce a favorable change in its course or, in other words, to cure the patient. I never attribute therapeutic powers to a medicine unless I observe its employment to be invariably and constantly followed by some change in the morbid products and by the termination of the disease in a shorter time than when it is allowed to undergo spontaneous involution.

In these days of blanket diagnosis and routine systems of treatment when the proponents of the all-embracing concepts of neurodermatitis and psychosomatic disease are attempting to break down distinctions between diseases and to sweep them all into amorphous modern versions of the ancient humors and dyscrasias, Hebra's voice is sadly needed.

On the subject of scabies Hebra the clinician wrote a chapter to which nothing need be added (with the exception of benzyl benzoate) to bring it up to date in 1947. At a time when scabies had been universally treated as a systemic disease, with sufficient lack of success to make it the most common of all diseases of the skin, he determined by extensive experiments that scabies was caused by the local action of the itch mite, confirming the forgotten discovery of Bonomo in 1687. His description of the various clinical features of scabies, the life cycle of the itch mite and the various methods of treating the disease produced one of the classics of medical literature.

To the complex study of eczema Hebra brought the revolutionary knowledge, evolved from experimentation with external irritants, that

1. Hebra, F.: On Diseases of the Skin, London, The New Sydenham Society, 1868, vol. 2 p. 19.

all the inflammatory changes in the skin can be produced by purely external causes. He thereby focused the attention of dermatologists on the skin as an organ of local as well as systemic disease. He did much to free the specialty of dermatology from the stifling dogma of constitutional dyscrasias which had so long obstructed progress toward rational diagnosis and treatment.

In general it may be said that diseases do not change; only our understanding of what is happening is subject to reinterpretation. It is a tribute to the care with which Hebra and other great clinicians of the past examined their patients, studied and classified their dermatoses and appraised the effect of treatment that even today we lean so heavily on the foundations of clinical dermatology which they built for us.

How can one develop clinical judgment? The basic ingredient is thorough examination of patients. An experienced clinician can often make a diagnosis after a fleeting glance. Into that glance, however, is poured the sum total of all his experience focused sharply on the interpretation of the problem at hand. The beginner has no such collection of clinical pictures in the file of his memory to draw on. For him each case is a new mystery the clues of which he must uncover one by one. He must school himself in the rigid discipline of some definite system for examining every patient. Only by searching for all possible evidence in each case can he guard himself against the risk of overlooking some one minute clue that may prove to be decisive. There is no basic training of greater value than the careful observation and description of morphologic data. It is the dermatologists' great fortune that the lesions which they examine are actually gross pathologic specimens so located on the surface that they can readily be examined during life. Let dermatologists then, like pathologists, examine minutely and describe thoroughly. Acquired early, the habit of such careful scrutiny makes a student's training more fruitful, for a person sees only what he recognizes. One case which is examined critically and understood is worth many in which the lesions are not interpreted correctly. The gross examination of the eruption often needs to be amplified by magnifying the pathologic changes through microscopic sections. In some diseases, as in tumors, such microscopic examination is essential to the diagnosis; in most, however, it merely offers additional clues for the differential diagnosis. At times one needs to draw on the aid of all possible laboratory procedures to elicit information that may aid in the diagnosis and treatment in a case. But at no time can the practice of dermatology become a laboratory science. All laboratory tests are fallible, and, again, the results of all laboratory procedures must be sagely evaluated. In all phases of his training the student should have the guidance of a dermatologist of experience so that all the facts which he masters may be valid and all his habits well grounded. For the

final stage of his training there is no better finishing school than the association with a qualified preceptor. It is to be hoped that additional preceptorships will be established, so that in time every student will have the benefit of this type of guidance.

Since our aim in training dermatologists is primarily to develop good clinicians, it necessarily follows that our teachers must be good clinicians. To help students to develop those powers of observation and reasoning that are necessary for good clinical judgment, a teacher must himself be the master of those virtues. He must be able to point out all features of a disease and to appraise them objectively if he is to train good clinicians. He must also practice what he teaches. If his interpretation of clinical findings is based on unfounded theories or is influenced by his own emotional difficulties, or if his practice is tinged with fads, his students will either follow him blindly into uncharted seas or they will disbelieve all he teaches. It is a heavy burden to have the responsibility of helping to mold an inexperienced mind. It is a responsibility not to be assumed lightly or capriciously. The preceptors of old chose their apprentices with care, so that the few opportunities available were given to men who were thought capable of using them well. For the sake of the students of today the same care should be exercised everywhere in selecting the few who are to teach them. By the proficiency of the teachers and preceptors who are chosen and by the quality of instruction which is given we are fixing the level of the dermatologists who will follow us.

Finally, what is the role of the clinician in the investigative field? It is true that most epoch-making advances in science have been made in the field of pure research, that is, research not directly applied to some practical end. But even pure research, as exemplified by the problem of nuclear fission, was spurred to successful completion years ahead of its time by the practical necessity of producing an atomic bomb in a competitive race for time. So in the field of dermatology many important contributions were made with the direct aim of clinical application. To mention but one, Ehrlich performed his ingenious experiments with organic arsenicals in a deliberate search for a drug to destroy Treponema pallidum.

Often great discoveries have had their origin in accidental observations. Fleming's chance discovery of the antibiotic action of the mold Penicillium would have been just another interesting observation were it not for the utilization of this phenomenon in clinical medicine. By its extensive exploitation in all fields of medicine this discovery ushered in a completely new era of antibiotic therapy that still has many developments to unfold.

In 1895 Roentgen noticed that radiations from a Crookes tube produced fluorescence in a piece of paper coated with barium platino-

cyanide even when the tube was covered to intercept the ordinary light emanating from it. Within a few months this accidental discovery was translated into the practical application of using roentgen rays to diagnose fractures and to locate foreign bodies. The effect of roentgen rays on living tissues was also soon noted, and the first case of malignant disease which was successfully treated by roentgen rays, a rodent ulcer, was demonstrated by Stenbeck of Stockholm, Sweden, in 1899.[2]

Even more frequently advances have been made by observing and investigating customs that have been handed down through the ages. For centuries infusions of cinchona bark had been used successfully in the treatment of chills and fever. Eventually quinine was isolated from cinchona and was found to be a specific poison for the Plasmodium of malaria. Ephedrine is a comparatively recent addition to our armamentarium for the treatment of allergic diseases, and it too was isolated from a crude drug, ma huang, that had been widely used for centuries in China.

A good clinician permits himself to learn from his patients by observing with an unprejudiced mind the clinical experiments which they, at times unwittingly, perform. While still a boy, Jenner learned from neighboring farmers that an attack of cowpox prevented infection with smallpox. He performed his first inoculation with cowpox in 1796 and, after two years of successful experimentation, applied to the Royal Society for permission to present his observations before them. His request was rejected with the advice that he "ought not to risk his reputation by presenting to the learned body anything which appeared so much at variance with established knowledge and withal so incredible." It is the mission of the clinical investigator to work to free the established knowledge of his time as rapidly as possible from outworn prejudices and dogmas.

In all fields of medicine revolutionary changes in longheld concepts have occurred when clinicians have adjusted the pattern of their thinking to conform with the facts which were taught them by their patients. Since time immemorial patients with heart failure were put to bed in spite of the general experience of such patients that it was difficult to breathe while lying down. Their attacks of suffocation generally occurred in bed, and relief could be obtained only by their sitting up or walking around the room. Often patients with heart failure would be seen with edema of the legs and feet. Soon after being put to bed such patients would lose the swelling of the lower extremities but would experience hydrothorax. The inferences from these simple observations were obvious: that fluid in the legs might be unsightly but that fluid in the lungs was suffocating and often fatal,

2. Cited by Pusey, W. A., and Caldwell, E. W.: The Practical Application of the Röntgen Rays in Therapeutics and Diagnosis, Philadelphia, W. B. Saunders & Co., 1903, p. 403.

and that placing a patient with heart failure on his back merely moved the fluid from the lower to the upper part of the body. It is only in the last few years, however, that these obvious truths have been recognized, and such patients are now being treated more successfully by being kept in a chair during the day and propped up in a tilted bed at night. This clinical reorientation was the contribution of Samuel A. Levine, whose recent paper, "The Treatment of Congestive Heart Failure," [3] I can recommend as stimulating reading even for dermatologists, for it is a masterly exposition of the importance of clinical observations in differential diagnosis that could well be transposed into our own work.

In all research having as its aim the solution of clinical problems, good clinical judgment must be relied on to guide the work. How can one evaluate the effect of various treatments on, let us say, cases of neurodermatitis if eventually there is some question about the actual diagnosis in the cases under scrutiny? Investigations into causative factors in cases of supposed cutaneous allergy, for another example, can have but little value if the patients are discovered later to have been suffering from scabies, pityriasis rubra pilaris or some other nonallergic disease. Finally, a clinician must be "accurately acquainted with the complaint" in all its many clinical variations before he may correctly evaluate the effect of the experimental factors that he has introduced.

In dermatology, as in all fields of medicine, it is the privilege of the few to make discoveries that will bring benefits to unknown multitudes. It is, however, the opportunity of every dermatologist to bring comfort and relief from suffering to each of the individual patients with whom he has personal contact. This opportunity carries with it the responsibility to make himself skilled in all methods of diagnosis and treatment that may qualify him for this task, the duty to make of himself a good clinician.

1905 Field Annex Building.

3. Levine, S. A.: The Treatment of Congestive Heart Failure, Proc. Inst. Med. Chicago **16**:214, 1946.

ELECTROLYSIS VERSUS HIGH FREQUENCY CURRENTS IN THE TREATMENT OF HYPERTRICHOSIS

A Comparative Histologic and Clinical Study

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IN 1879 Michael [1] introduced the use of electrolysis for the permanent removal of hair, and since then it has been the method generally employed by dermatologists. According to Kovacs [2] the hair follicle is destroyed by electrolysis in the following manner: the sodium ions have positive charges and go to the negative pole (the needle) where they lose their charges and react on the water in the tissue to form sodium hydroxide (NaOH) and liberate hydrogen. The sodium hydroxide in turn destroys the cells adjacent to the needle. Hand [3] introduced a new type of apparatus equipped with a "switch" designed to decrease the shock and burning caused by rapid "make and break" of current. Marton [4] attempted to improve the rapidity of the operation by using multiple needles, but Cipollaro [5] disapproved of the use of more than one needle because of the difficulty of trying to insert properly into the follicles and to control at the same time eight to twelve needles. He suggested that the operator of multiple needles frequently inserted the needle into the skin but not into the follicle. Niemoeller,[6] who is not a physician, in 1938 published a book in which he reviewed the various methods of treating superfluous hair.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 11, 1946.

1. Michael, C. E.: Trichiasis and Distichiasis: Reflections upon Their Nature and Pathology, with a Radical Method of Treatment, M. J. St. Louis Cour. Med. **1**:121, 1879.

2. Kovacs, R.: Minor Electrosurgery, M. Rec. **155**:163-165 (March 4) 1942.

3. Hand, E. A.: Electrolysis: Introduction of an Instrument for Relatively Painless Treatment, Arch. Dermat. & Syph. **45**:1094-1100 (June) 1942.

4. Marton, M. H.: Treatment of Hypertrichosis by Improved Apparatus and Technic, Arch. Phys. Therapy **21**:678-683 (Nov.) 1940.

5. Cipollaro, A. C.: Electrolysis: Discussion of Equipment, Method of Operation, Indications, Contraindications, and Warning Concerning Its Use, J. A. M. A. **111**:2488-2491 (Dec. 31) 1938.

6. Niemoeller, A. F.: Superfluous Hair and Its Removal, ed. 1, New York, Harvest House, 1939.

In 1924 Bordier [7] recommended diathermy for the removal of superfluous hair. Kovacs [2] stated that the principle of the action in all high frequency electrosurgical methods is an intense concentration of current under a small active electrode. This results in a destructive thermal effect around the needle, which leads to instantaneous coagulation of the albumin of the tissues.

According to some investigators, diathermy allows the operator to remove the hairs more rapidly, with less pain and with good cosmetic results. Rosenberg and Smith [8] were of the opinion that the cutting current resulted in less scarring than that produced by electrolysis, and they considered that there was little chance of recurrence as the greatest amount of heat was concentrated at the point of the needle, which should be inserted into the hair papilla. Karp,[9] Goodman [10] and Derow [11] stated that surgical diathermy had a "cone effect"; i. e., the burned area was in the shape of a cone radiating from the point of the needle, and thus the papilla could be destroyed without scarring even if the point of the needle was only near the base of the hair follicle. Gross [12] doubted that the "cone effect" occurred but stated that diathermy was relaxing to the operator and gave good cosmetic results. Gara [13] preferred coagulation by long wave diathermy. He used a bipolar current at 10 to 60 milliamperes for one to two seconds. He noted that recurrence varied from 20 to 40 per cent and at times to 60 per cent, with an average of 30 per cent. Karp,[9] Derow [11] and Lerner [14] stressed the fact that there was little or no recurrence in their patients. All the advocates of the diathermy method claimed that there was practically no scarring when operators used the proper machine and technic. Savill,[15] on the other hand, favored electrolysis over diathermy for the removal of hair. She acknowledged that recurrence may be as frequent with electrolysis but stated the belief that scarring is more likely to ensue after diathermy.

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7. Bordier, H.: Technique de l'épilation diathermique, Monde méd., Paris **42**:78-81 (Feb. 1) 1932.

8. Rosenberg, W. A., and Smith, E. M., Jr.: Removal of Superfluous Hair with the Cutting Current, Arch. Phys. Therapy **24**:277-279 (May) 1943.

9. Karp, F. L.: High Frequency Current in the Treatment of Hypertrichosis, Arch. Dermat. & Syph. **43**:85-91 (Jan.) 1941.

10. Goodman, H.: Non-Surgical Reparative Dermatology or Electro-Medical Cosmetology, Urol. & Cutan. Rev. **46**:726-727 (Nov.) 1942.

11. Derow, D.: Short Wave Epilation, Arch. Phys. Therapy **20**:101-102 (Feb.) 1939.

12. Gross, P., in discussion on Lerner.

13. Gara, G.: Hypertrichosis: The Problem and How to Handle It as It Appears in the Every-Day Practice, Urol. & Cutan. Rev. **45**:771-774 (Dec.) 1941.

14. Lerner, C.: Essentials in the Art of Epilation for Hypertrichosis, M. Rec. **151**:193-194 (March 20) 1940; The Treatment of Hypertrichosis by Electrocoagulation, New York State J. Med. **42**:879-882 (May 1) 1942.

15. Savill, A. F.: The Hair and Scalp: A Clinical Study, with a Chapter on Hirsuties, London, Edward Arnold & Co., 1935, p. 274.

In 1942 Erdos-Brown [16] reviewed the literature on high frequency currents for the removal of hair and stated that vacuum tube diathermy is superior to the spark gap machine, because the former generates a sustained undamped current which flows smoothly in equal bursts of intermittent wave trains. She noted that an exposure of five hundredths to twenty hundredths of a second with a low current would destroy the papilla. She stated, "It is possible to perform epilation with the spark gap diathermy machine, but two electrodes are necessary, and one of these must be a directly applied and tightly bandaged metal applicator." With the vacuum tube current it is not necessary to use the directly applied metal secondary electrode. She observed that a few hairs returned after removal and stated, "Scar formation may be caused by too short a space of time between the treatments, too small interspaces between hairs or overdosage." She considered epilation with diathermy superior to epilation with electrolysis, as it caused less discomfort, was instantaneous, could not cause tattooage, and gave excellent cosmetic results and there was only occasional recurrence.

After employing electrolysis for ten years for the removal of superfluous hair, I was so impressed by the article by Erdos-Brown that I obtained a high frequency tube machine of the same make that she had used. Erdos-Brown [16] illustrated (on page 499) by a diagram the hook-up of the vacuum tube machine, which will not be repeated here. This machine is satisfactory for desiccating, coagulating and cutting operations. I used this machine over a period of eleven months for one hundred and twenty treatments. Four patients were given more than ten treatments and eight or nine treatments were administered to 4 others.

The power dial on the machine was not calibrated but had the words "increase power" in the center of the face of the dial. The power indicator was set at the letter "r" in the word "power" on the dial. In removing hairs with the monopolar short wave the current was turned on by tapping a foot switch. It was difficult to determine the exact time the current was on. The average rate was about two taps per second. It required twenty to thirty taps on the foot switch before a hair loosened. This consumed an average of ten to fifteen seconds. Then at least five seconds passed from the time that the needle was withdrawn and reinserted into another follicle and the current was again turned on. Therefore, approximately one hundred and twenty hairs could be removed in thirty minutes, if the operator worked rapidly.

The time consumed in removing hair with electrolysis varies greatly with the type of hair, the tolerance of the patient and the intensity of the current used. With 1¼ milliamperes the average was twelve seconds

16. Erdos-Brown, M.: Superfluous Hair: Removal with the Monopolar Diathermy Needle, Arch. Dermat. & Syph. **46**:496-501 (Oct.) 1942.

on intermediate hair, but with weaker currents and terminal hairs the time might have to be increased to sixty seconds. The average interval required to pull the hair out and reinsert the needle was approximately five seconds. In one-half hour about forty hairs could be removed.

EXPERIMENTS WITH AN ANIMAL

EXPERIMENT 1 (electrolysis).—The hair of a full-grown rat was shaved with an electric razor. The rat was anesthetized with veterinary pentobarbital sodium and was placed on the moistened positive electrode. The needle was inserted 2 or 3 mm. at a right angle to the surface into the skin in the shaved area. One milliampere of current was applied for thirty to sixty seconds. A biopsy was made immediately and the sections stained with hematoxylin and eosin.[17] Although the specimen was cut serially it was difficult to find the track of the needle, because the changes produced were not prominent. Only the areas showing the most advanced changes are portrayed in the photograph.[18] The lesion was almost as large as a high power field. The epidermis was attached and the cell borders indistinct. Some pyknotic nuclei were visible. In the center of the altered area the collagen had a blue tinge and contained granular strands and cell debris. Surrounding this area the tissue was more eosinophilic and contained many cells with nuclei which were slightly distorted and more basophilic than the nuclei of the normal cells (fig. 1 *A*).

EXPERIMENT 2 (intermittent monopolar short wave).—The needle attached to the coagulating pole of the short wave machine was inserted 2 to 3 mm. into another shaved area of the same rat in a manner similar to that in experiment 1. The rheostat was set at "r," and ten to twenty half-second exposures were given. A biopsy was made, and the sections were stained with hematoxylin and eosin (fig. 1 *B*). The affected area was saucer shaped and slightly larger than a high power field. The cells of the epidermis were deep blue, and most of the nuclei could not be delineated. The collagen was of a deep basophilic color in homogeneous broad ribbons or chunks, containing only a few pyknotic nuclei.

EXPERIMENT 3 (continuous monopolar short wave).—Monopolar continuous one second exposures with the same settings as in experiment 2 resulted in similar lesions with more severe changes. The collagen bundles were confluent and more basophilic than in experiment 2. The shape of the lesions was the same as that of the lesions caused by multiple shorter exposures.

EXPERIMENT 4 (bipolar short wave).—The same exposures were given as in experiment 2. The same severe alterations in the cutis resulted as those observed in experiment 3, but the changes were over a larger area (three fourths of a low power field).

EXPERIMENTS WITH HUMAN SUBJECTS

In the experiments with human subjects, tissue was obtained at autopsy from the pubic area. Two adjacent circles, A and B, were drawn with ink on the skin. The monopolar short wave was applied to hairs for a half-second or less for ten to twenty exposures in circle A, and in circle B hairs were treated with electrolysis with ¾ milliampere for about forty to sixty seconds. Treatment was

17. The serial sections were made in the Department of Dermato-Histopathology of the Johns Hopkins Medical School.

18. All photographs were taken to show the most severe changes caused by the different modes of current.

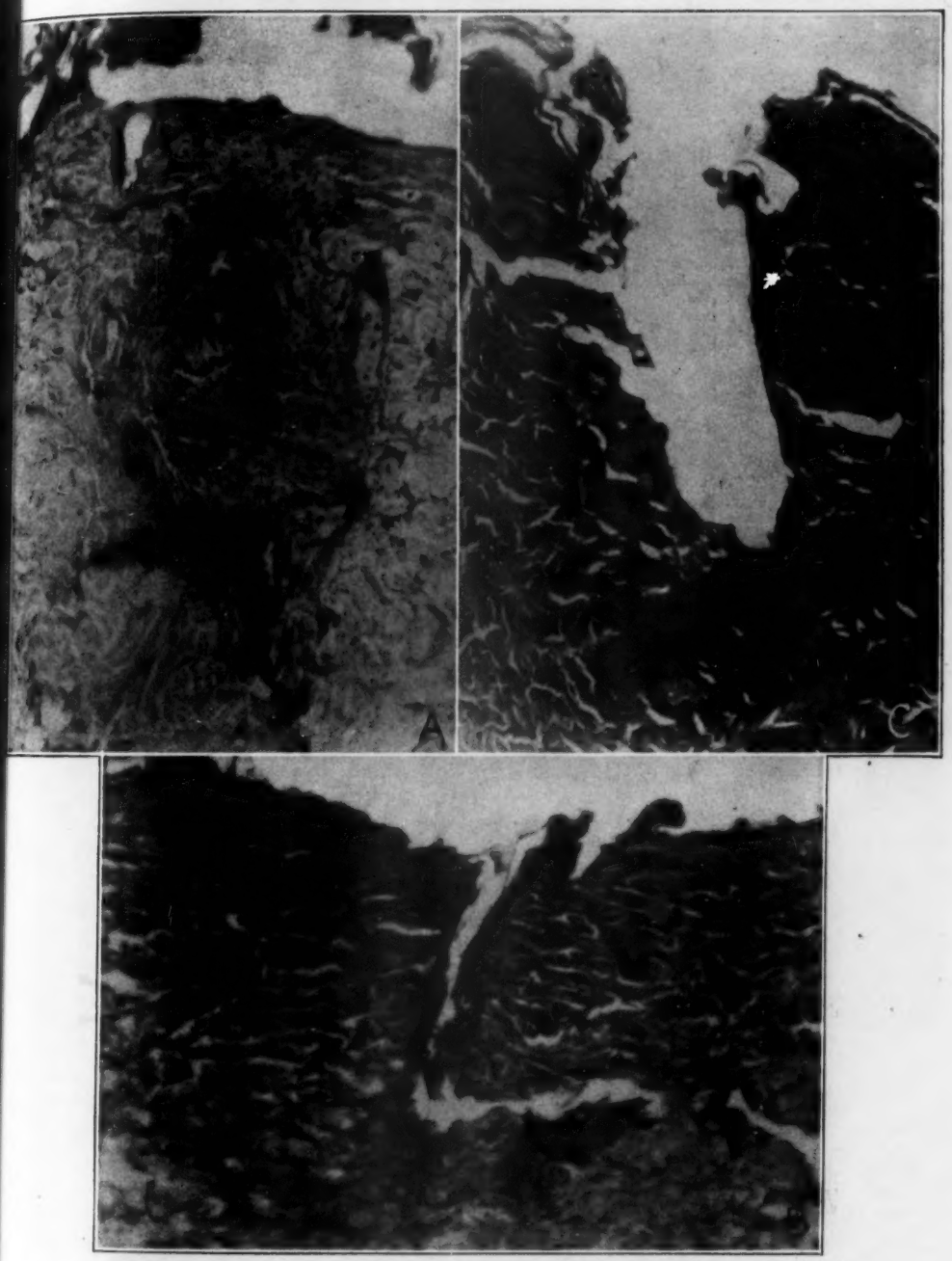

Fig. 1 (rat tissue).—*A*, mild destructive changes from the electrolysis. The true architecture of the skin is readily discernible. *B*, extreme burning of the tissue in the shape of cylinder with the needle as the axis from the vacuum tube type of high frequency current. *C*, destruction of the desiccated tissue by spark gap high frequency current similar to that obtained with the vacuum tube machine.

Fig. 2 (human tissue).—*A*, the follicular destruction resulting from the use of electrolysis is confined principally to the follicle and its orifice. The perifollicular alterations are mild. *B*, a nonfollicular lesion resulting from treatment with electrolysis shows a wide zone of edema and a small area of destruction of the epidermis surrounding the puncture from the needle. The alterations in the collagen are mild.

administered in each area until the hair slipped out easily. On the examination of the serial section it could not be determined whether the minor changes seen were due to either method. The changes in the tissue were so slight that it was difficult to tell which follicles had been treated. The experiment was repeated, and the short wave was applied continuously for one to two seconds. Again the microscopic examination of serial sections was unproductive of information regarding damage to tissue.

ELECTROLYSIS (experiments on a living human subject).—An area on the chest of a white man aged 48 was anesthetized with 2 per cent procaine hydrochloride, and eight hairs of the terminal type were removed with electrolysis. The current

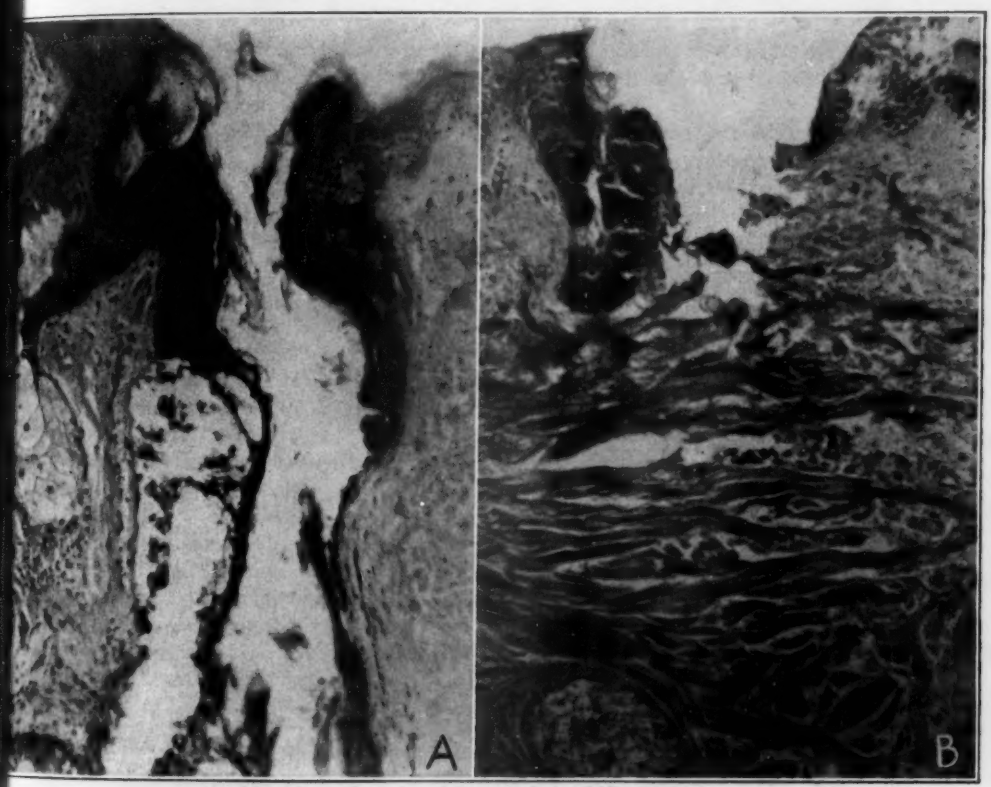

Fig. 3 (human tissue).—*A*, follicular changes due to treatment with vacuum tube high frequency current. In spite of the relatively strong current the destruction of the follicle is not complete. *B*, a nonfollicular lesion from the use of vacuum tube high frequency current. The changes in the epidermis are more destructive, but not as extensive as after electrolysis. Note that the zone of desiccation takes the form of a cylinder and not a cone.

was set at 1¼ milliamperes, and the average time necessary for a hair to loosen was forty-five seconds. The needle was introduced into several nonfollicular areas, which were treated in a similar manner. A biopsy of each treated area was made immediately. The specimen, after fixation in a solution of formaldehyde, was cut into serial sections which were stained with hematoxylin and eosin.

In the area through which the needle passed, i. e., through the follicular canal and out through the base of the follicle, the histologic changes were as follows: The epidermis in the follicular orifice and for a distance of about 460 microns in diameter was depressed and distorted (fig. 2 *A*). It contained narrow bands of dark blue conglomerate masses of pyknotic nuclei. The follicular wall was replaced by a fine granular, slightly basophilic core of material. These changes extended down through the racemose sebaceous gland under the follicle. In a nonfollicular lesion, surrounding the depression where the needle was introduced, the epidermis for about 1,000 microns was edematous and contained intraepithelial vesicles (fig. 2 *B*). Below the epidermis the burned core of collagen was approximately the same width at the bottom as at the top, i. e., about 500 microns.

Short Wave.—In an adjoining area of skin on the same subject about eight hairs were treated with the vacuum tube machine with a monopolar coagulating current with ten to fifteen approximately half-second exposures and others by continuous two second exposures. The needle was inserted also into several nonfollicular areas, which were given continuous two second exposures at the same setting. A specimen for biopsy was taken from the treated area, was fixed in a solution of formaldehyde, stained with hematoxylin and eosin and cut serially in the same manner as the specimen from the area treated with electrolysis.

A treated hair follicle showed the following changes: The mouth of the follicle was wide, and the rete cells were not altered, but in the canal the lining cells were shrunken and had pyknotic nuclei or were replaced by a vesicle. The follicular wall was incompletely destroyed. The perifollicular tissue was unaltered, but the cells in the center of the underlying sebaceous gland showed signs of lysis, and the collagen below the gland was in basophilic bands (fig. 3 *A*).

Histologic examination of a nonfollicular lesion caused by high frequency generated by the vacuum tube machine showed the following features: The surface of the epidermis was depressed in the shape of a shallow funnel about 200 microns wide and about 160 microns deep. The rete cells lining this depression were shrunken so that little cytoplasm was seen and the nuclei were pyknotic. In the epidermis, in an area about the depression 830 microns in diameter, there were many small intraepithelial vesicles. Extending down through the dermis to the level of the sweat glands there was a zone of basophilic collagen, which was approximately 500 microns wide throughout its length. The collagen was in basophilic bands or chunks (fig. 3 *B*).

EXPERIMENTS WITH HIGH FREQUENCY CURRENTS GENERATED BY SPARK GAP MACHINES

Experiments with the high frequency current generated by spark gap machines were confined to the rat's skin or to small human tumors before their complete removal and to the skin of a few clinical patients who were treated for the removal of hair. Two different makes of machines were used. The lesions which resulted were of the same general shape, intensity and quality as of those due to short wave. About 10 microns of tissue immediately around the needle had a tendency to stick to the needle and pull away when the electrode was extracted (fig. 1 *C*).

A summary of the comparative histologic changes which resulted from treatment with diathermy and electrolysis shows that the affected areas on the surface and the crater depressions in each case were similar, but may be smaller after diathermy. The rete cells of the follicle can be destroyed as completely with electrolysis as with high frequency currents, but with the latter agent the cells are replaced by a denser, more basophilic material and the changes seem to be more destructive and irreversible. The surrounding collagen was affected less with electrolysis than with short wave, and the changes were less basophilic and more granular. Experiments with tissue removed from a cadaver gave unsatisfactory results with either electrolysis or short wave.

INSULATED NEEDLES

It has been shown by histologic studies that after treatment with electrolysis or desiccation the greatest destruction of tissue occurs on or

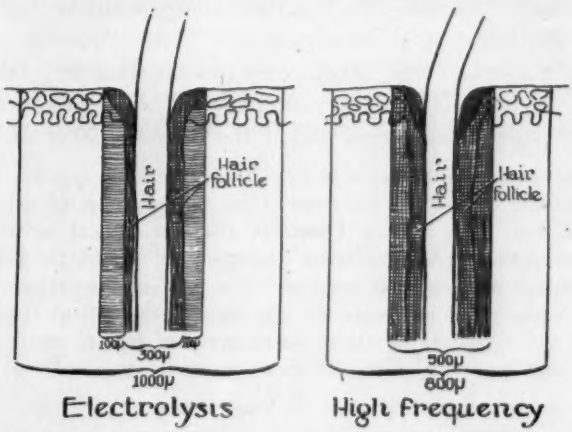

Fig. 4.—Schema showing the relative quantitative and qualitative destructive changes caused by the two types of currents in relation to the hair follicle.[19]

near the surface. There may be an advantage, therefore, in the use of insulated needles. Bordier [7] used a needle designed with an elliptic point and insulated in such a manner that only the tissue surrounding the papilla was desiccated. Bordier claimed that with his insulated needle the borders of the orifices of the follicles were not injured, while the hair papilla and the surrounding area were desiccated. Consequently, the destroyed follicles healed without visible scars.

An insulated needle must be introduced to the proper depth to be effective. The noninsulated part must pass beyond the papillary layer, but if it is inserted too deeply it will not burn the papillae of the hair follicles. The depth varies with the size of the follicles, and it is not

19. This illustration is from the Art Department of the University of Maryland School of Medicine.

always possible for even an experienced operator to be certain that the needle is inserted too far or not far enough.

Two types of insulators have been used. One is a sheath over the needle excluding the point, and the other is a coating on the needle leaving the point of the needle exposed. Needles covered by sheaths frequently break at the point where the needle leaves the sheath. A sheath increases the diameter of the needle, and it is difficult to insert it into the follicle. A coating of insulation increases slightly the diameter of the needle, but with use the coating wears off. If the insulating material is colorless, it is difficult to determine how much of the needle is coated or how deeply the needle is inserted. These additional sources of error may increase the number of hairs that recur after treatment.

REPORT OF CASES

In an editorial in the *Journal of Clinical Endocrinology*[20] it is contended that: "Electrolysis is an unending business and apt to be scarring if the beard is at all luxuriant." The following 2 cases are reported to illustrate that satisfactory results can be obtained with electrolysis in patients with severe hypertrichosis (terminal type of hair) if the patient perseveres and if the operator is careful.

CASE 1.—A patient with severe hypertrichosis (terminal type of hair) involving the mandibular regions and the front of the neck was treated with electrolysis once a week from June 1938 to December 1940 for a total of seventy hours. From 1940 to 1943 she received seven treatments to destroy the hairs that had recurred. Only slight scarring resulted. She was able to tolerate 1½ milliamperes of current. Before treatment was started, the patient shaved or spent half an hour a day rubbing an emery board over her face to control the growth of hair, but after treatment there was no return of the terminal type of hair.

CASE 2.—A patient was not able to tolerate electrolysis with more than ¾ milliampere of current. It was difficult to determine just how much hair of the terminal type was present, because she used depilating wax each week to remove the protruding hairs. She was treated from November 1941 to October 1944 for a total of eighty treatments. In 1945 she returned once a month for the purpose of having an occasional slight regrowth destroyed, whereas previously the hair on the chin and neck was so excessive that it could be treated each week. No visible scars are present. If the patient had been able to tolerate treatments of 1½ milliamperes of current, half the number of sessions would probably have given satisfactory results.

The question of pain is important in the treatment of patients with hypertrichosis. If a patient tolerated electrolysis therapy poorly, she usually complained of much pain or discomfort when treated with the diathermy current. Some patients seemed to have no discomfort. Many of them complained of some pain in the first treatment. The

20. The Endocrine Puzzle of Heterosexual Hypertrichosis (Hirsutism), editorial, J. Clin. Endocrinol. **3**:426-427 (July) 1943.

discomfort usually decreased with subsequent treatments. Seldom was the pain so intolerable that the patient would discontinue treatments.

COMMENT

Electrolysis causes destruction of tissue by lysis due to local decomposition of tissue, which frees an alkali at the negative pole, the needle. High frequency currents generated by vacuum tube or spark gap machines cause destruction of tissue by the heat generated by the electric current concentrated at the needle electrode.[2] Electrolysis is slow, tedious and time consuming. Although there is a high percentage of recurrences when electrolysis is employed, it is considered to be more satisfactory than high frequency currents. Treatment with electrolysis rarely causes abscesses, and those that occur are always superficial and heal with imperceptible scarring. Deeper abscesses and depressed scars developed in several patients treated with short wave. It was my impression that most of the hair removed with high frequency currents apparently recurred unless the current was kept on long enough to cause visible burns, which healed with depressed scars. About ninety hairs from each breast of 1 patient were removed with diathermy at least three times over a period of three months, yet after several months all hairs had apparently recurred.

TECHNIC

A few points concerning the usual technic of treatment with electrolysis for hypertrichosis are listed. The patient grasps the moistened positive electrode. The needle (negative pole) is held by a needle holder which has a switch, and the current is turned on by the operator after the follicle is entered. A milliamperemeter is always used, and the current is adjusted to the tolerance of the patient (½ milliampere to a maximum of 1½ milliamperes). Most operators agree that with either method the needle should be kept in the follicle with the current on until the hair slips out without any resistance, but when the hair loosens the entire follicle may not be destroyed.

It has not been accurately determined how much of the follicle can be left intact without the hair's regrowing. Also it is not known whether the hair follicle can regenerate only from the papilla and whether it can regenerate when a part of the wall is not destroyed. Therefore two recommendations for the treatment of persons with hypertrichosis are made to increase the efficiency of electrolysis. It is suggested that the current be continued for about ten seconds after the hair slips out without application of traction. When a hair regenerates it usually regrows with the same texture, color and shape as the original hair. Since hair follicles when partly regenerated may be more readily destroyed than when allowed to obtain their full growth,

it is suggested that patients return at regular short intervals so that the regenerating follicle can be treated before it attains its full growth.

SUMMARY AND CONCLUSION

Comparison of histologic changes caused by treatment with diathermy and electrolysis showed that the alterations in the epidermis were similar in shape but were more intense or severe after treatment with diathermy. The rete cells of the follicle could be destroyed as completely by treatment with high frequency as with electrolysis, but with the former agent the cells were replaced by a denser more basophilic material and the changes seemed to be more destructive and irreversible.

Most of the hairs removed with high frequency currents recurred unless the current was sufficiently intense or was applied long enough to cause visible burns which tended to heal with depressed scars.

The lesions caused with high frequency currents took the shape of a cylinder and not that of a cone.

NOTE.—Dr. Murry M. Robinson (Removal of Superfluous Hair by Monopolar Coagulation, *M. Ann. District of Columbia* no. 11, **15**:531 [Nov. 1946]) stated that with the diathermy current he has demonstrated that a cone effect is obtained. "The 'coagulation' forms a cone with the apex at the point of the needle and the base at the surface of the skin, so that with a steadily applied current, destructive action will occur at the surface of the skin and produce visible scarring; whereas with the current applied in short bursts the action takes place only at the papilla and its immediate surroundings, and the surface of the skin is left unaffected." Unfortunately, his photomicrographs do not demonstrate the cone-shaped area of destruction.

8 East Madison Street.

ABSTRACT OF DISCUSSION

CAPTAIN ROBERT L. GILMAN, Memphis, Tenn.: I do not believe that Dr. Ellis needs to apologize or be diffident in the opening of his paper because it concerns a process that, no doubt, all of us, without exception, have used. I do not imply that we have been familiar with it, but we have certainly used it with familiarity.

I was struck by Dr. Ellis' conclusions, which I arrived at by a different route, as many of us have. Dr. Ellis seemed to be the first investigator to prove by painstaking work his point that treatment with electrolysis is superior to treatment with diathermy in the permanent removal of hair. That has been my observation.

I note that he had less recurrence and fewer complications with electrolysis. After removing pigmented hairy moles with the short wave machines, satisfactorily and without leaving a disfiguring scar, I have observed that many times a few hairs will remain, regardless of the amount of current used.

Most women and young girls to whom I have given this treatment seem to be particularly immune to pain and peculiarly indifferent to minor scarring. Many times I have seen results with which I was entirely dissatisfied, but which satisfied the patients. However, I still think that we should use a process, such as Dr. Ellis has described, that gives the fewest recurrences, the best appearance without scars and the minimum amount of pain.

Dr. Ellis is to be congratulated on presenting a subject which we are likely to dismiss sometimes, because of our apparent familiarity with it, but which is important.

Dr. Paul E. Bechet, Elizabeth, N. J.: I also enjoyed Dr. Ellis' presentation. I have had the same results from treatment with high frequency current in patients with hypertrichosis as Dr. Ellis has had, and I have returned to the use of electrolysis. I do not know whether the untoward results which I observed occurred because of the rapidity of the action of the high frequency currents, but I am sure that results in my patients in relation to permanency, lessened pain and cosmetic effect were better in treatment with electrolysis than with high frequency current.

Dr. Ellis gives credit to Dr. Charles E. Michael, of St. Louis, for the discovery of the method. In this he is only partially correct. Michael used the method for the first time in 1875, but only for the destruction of "wild hairs" of the eyelids. It was William A. Hardaway who first introduced treatment with electrolysis in dermatology in 1877, but with his predilection for historical and biographic accuracy, as well as his innate fair-mindedness, he never wrote an article on electrolysis without giving due credit to Charles E. Michael.

Dr. Anthony C. Cipollaro, New York: Dr. Ellis deserves to be congratulated on doing detailed and intricate research. He was kind enough to send me a copy of his paper before the meeting, which I read and studied carefully, and I prepared a discussion, but before reading my notes I should like to discuss three things which he emphasized.

First, regarding the apparatus he used, most of the work was done by the tube machine, and we have observed that tube high frequency machines are not so suitable for this type of work as spark gap machines, which produce a damped current. Perhaps these are, in part, the reasons that his treatments have not been particularly effectual.

I agree with Dr. Ellis in his statement that high frequency currents produce a cylindric type of destruction. Dr. MacKee and I published photographs in "The Principles and Practice of Physical Therapy" in 1932 showing that type of destruction, and, with your permission, I should like to show you a slide to illustrate this.

Dr. Ellis has emphasized the fact that the coagulating current is too destructive in epilation. Destruction of tissue with high frequency currents is dependent on two factors: the strength of the current and the duration of the application. It is a multiple of the time and the amount of current, so that if one uses a little time and a lot of current one will get a great deal of destruction, or, also, if one uses a little current and a lot of time one will get a great deal of destruction.

In the main I agree with everything that Dr. Ellis has said. There are a few points on which I should like to elaborate. Dr. Ellis has quoted me as disapproving the use of more than one needle in treating patients with hypertrichosis with the galvanic current. I oppose the multiple needle technic because, first, it is difficult to hold in place and control more than one needle

at a time, and, second, when more than one needle is used there is an unequal distribution of current among the several needles. If thirty-six needles are used, as recommended by at least one person, the current in one needle may be one hundred times stronger than in an adjacent needle. Therefore, in addition to the technical difficulty of controlling more than one needle at a time there is an objection to the use of multiple needles based on distribution of current.

For routine purposes I advocate the use of high frequency current for the treatment of patients with hypertrichosis. However, the most important thing, to my mind, is to have equipment which is manufactured for this specific purpose. Many dermatologists make the mistake of thinking that any equipment for the use of high frequency current is suitable for treatment of patients with hypertrichosis. It is not, because in some equipment the current cannot be cut down enough to destroy the follicle without also destroying a great deal of surrounding tissue.

Also, a biterminal electrode should be used. The disperser electrode can be held in one hand, since the active electrode is the needle.

Dr. Ellis has mentioned that it took fifteen seconds to destroy some hair follicles with one type of diathermy apparatus which he used. I think that this type of apparatus is entirely unsuitable for such work. It should not take more than one or two seconds to destroy a hair follicle when the proper machine and the proper current are used. I base this statement on results which I have had during the last fifteen years using different types of high frequency currents.

I prefer high frequency current to galvanism for the treatment of patients with hypertrichosis because with high frequency currents more hairs can be removed per unit of time. I have not seen an abscess or a furuncle develop in a patient when the work has been properly done, either by me or by my associates at the New York Skin and Cancer Unit.

Treatment with either galvanism or high frequency currents causes pain. However, with high frequency currents the pain lasts for a second or so, whereas with galvanism the pain is less intense but is prolonged over a period of fifteen to forty-five seconds.

The matter of recurrence is important. So far as I am able to determine, there is no difference between treatment with high frequency current and with galvanism in the amount of hair which recurs. There is no way in which we can accurately determine the amount of hair which grows back. My guess is about 20 per cent after either method of treatment.

I am glad that Dr. Ellis has shown that there is cylindric destruction of tissue about the active electrode. I have already elaborated on that point. Scars can be severe with galvanism as with high frequency currents, but prevention of scars depends on the critical control of currents. Partially insulated or platinum needles offer no practical advantages. Needles made with jeweler's steel, such as are commonly used, have been satisfactory to most operators.

I do not doubt that hair can be successfully removed without causing scars with either the galvanic or the high frequency currents. However, the technic has to be faultless, and, unfortunately, not all dermatologists have taken the trouble to become experts in this phase of physical therapy.

I should like to take the opportunity here of condemning once more the use of roentgen rays, radium and other radioactive agents for the removal of superfluous hair. I want to emphasize it at this time because there are now, in Detroit and Chicago, establishments where superfluous hair is removed with roentgen rays. It seems to me that this is a revival of the old Tricho Institute

and that every dermatologist throughout the country should make all possible efforts to prevent the mushrooming of these establishments.

Another disconcerting incident has recently occurred. In November 1945, the patent office issued a patent for a so-called "x-ray razor." I examined the patent thoroughly, and it is nothing more than a roentgen-ray machine. The roentgen rays are filtered through a column of water enclosed within two layers of aluminum.

I congratulate Dr. Ellis on his presentation and thank him for giving me the opportunity for discussing this paper.

DR. DONALD M. PILLSBURY, Philadelphia: The matter of the permanent removal of hair and the study of Dr. Ellis have an importance which I think may not be generally appreciated, and that is in connection with war wounds. Many soldiers and sailors who have had to undergo extensive plastic procedures because of wounds may have skin grafts which come from areas which are hairier than the areas to which they are grafted, or there may occur, particularly on the face and sometimes on the scalp, unsightly tufts, or islands, of hair in the midst of scar tissue. The subject has been considered of such importance that there is a rather extensive study being done of the whole matter by the Surgical Division of the Surgeon General's Office. This study by Dr. Ellis, I think, is important from that standpoint.

DR. FRED D. WEIDMAN, Philadelphia: May I ask Dr. Ellis whether his sections showed any effects on the sebaceous glands in his subjects? The emphasis, naturally, is on the hair follicles, but I am curious to learn whether there was an effect also on the sebaceous glands. There is certain destruction of the epithelium of the common excretory ducts of the follicle and the sebaceous glands. I suppose that the answer is in the end result, namely, that (retention) sebaceous cysts do not follow this procedure, and I suppose that that implies regeneration of the epithelium in such a perfect way that it accommodates the secretion of the sebaceous glands.

DR. FRANCIS R. ELLIS, Baltimore: I wish to thank the discussers. Dr. Bechet is correct about Dr. Hardaway, and I think that most textbooks give him the credit.

As to the question raised by Dr. Weidman regarding the sebaceous glands, there is a liquefaction of the fats in the sebaceous glands near the needle, but the periphery of the glands is not affected. To prove what happens to the ducts, one may have to make a wax model from serial sections, as it is difficult to follow the ducts in the sections.

I have seen several patients with conditions similar to those mentioned by Dr. Pillsbury. The patients had skin grafts taken from a hairy region. One was a boy who had a burn across his forehead. The graft was made when he was a child, and when he became an adult a heavy growth of hair appeared in the graft.

I tried the Peerless machine a few times and made histologic sections from a specimen from 1 patient. The total amount of current depends on the time plus the intensity. I started with the settings at 30 and increased to 40 and finally to 50 on the two terminals, but histologic studies showed no changes in the hair follicles. The human experiment was a failure, due apparently to an error in technic. An experiment on a rat showed changes similar to changes which occur with the use of short wave.

I have repeated the human experiments with the Bovie apparatus, and I expect to continue these studies.

VITAMIN A IN DARIER'S DISEASE

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SINCE the first description by Darier [1] in 1889 more than three hundred and fifty papers have been published dealing with Darier's disease, a relatively rare condition, the cause of which, in spite of numerous investigations, remains undetermined. New knowledge of vitamin deficiency states brought promise of a fresh attack on the problem. Peck, Chargin and Sobotka (1941),[2] having noted the resemblance between the appearance of the skin in naturally occurring vitamin A deficiency and Darier's dyskeratosis, treated a patient with vitamin A and reported improvement. Since then many other patients have been similarly treated, many with benefit. The object of this paper is to describe our studies on the effect of vitamin A in 7 cases of Darier's disease and to compare our results with those of others. Brief notes of our own series of cases are as follows:

REPORT OF PRESENT SERIES OF CASES

CASE 1.—Mr. S., aged 33, had suffered from trouble with his skin since childhood, but otherwise his health was good. No other member of his family was affected so far as he knew. Examination showed typical Darier's disease, with pigmented, keratotic, partly follicular papules scattered over the body and limbs. They were most numerous on the neck, shoulders and sides of the trunk. Warty lesions were present on the backs of the hands. After three months' treatment with vitamin A many pigmented, keratotic plugs had disappeared, while others were smaller and lighter in color. The wartlike lesions on the backs of the hands remained unaffected, however. This man was then passed into the Navy as perfectly fit.

CASE 2.—Miss S., aged 30, has had trouble with her skin all her life. The appearance was that of severe Darier's dyskeratosis. The skin was dry, and

From St. John's Hospital for Diseases of the Skin, London, England.

1. Darier, J.: De la psorospermose folliculaire végétante, Ann. de dermat. et syph. **10**:597, 1889.

2. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223 (Feb.) 1941.

the characteristic brownish, hard papules were present in large numbers on the neck, arms, forearm, legs (particularly below the knees) and lower part of the trunk. The scalp resembled rather severe seborrhea. Flat, wartlike lesions were present on the backs of the hands, and minute follicular depressions were present on the palms. Her intelligence is low; she is an inmate of an institution for the mentally defective. She is a sister of the patient in case 4, and her father was found to be suffering from Darier's disease also, which he had first noticed in his seventy-fifth year. The familial relationship of these 3 patients is shown in figure 1, those affected being marked as black disks.

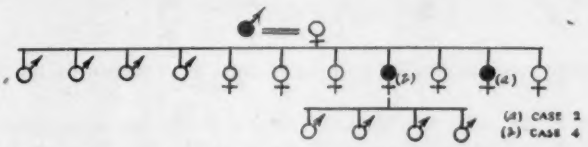

Fig. 1 (case 2).—Familial relationships of the patient in case 3. The affected patients are indicated by the black disks.

Unfortunately, her mental condition made dark adaptation tests valueless, and war conditions prevented estimation of the plasma vitamin A content, so that we do not know the state of her vitamin A nutrition before treatment was begun. A dark adaptation test on a normal sister gave a normal result. The wartlike lesions on the backs of the hands were not altered by treatment with vitamin A, though considerable improvement occurred elsewhere.

CASE 3.—Miss R., aged 9, had severe Darier's dyskeratosis. Pigmented papules were most distinct on the neck and calves, though present in large numbers on the forearms and elsewhere. Her intelligence was somewhat below normal. She

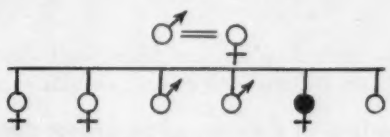

Fig. 2 (case 3).—Immediate familial relationship of Miss R. The patient is indicated by the black disk.

had been given small doses of vitamin A before we saw her. Her health is excellent, and no other member of the family has been affected by trouble with the skin. Her immediate relations are shown in figure 2.

CASE 4.—Mrs. P., aged 42, a sister of the patient in case 2, had well marked Darier's dyskeratosis, lesions being most plentiful on the scalp, neck and trunk and present to a lesser degree on the limbs. Her mental condition is subnormal, making her unsuitable for dark adaptation tests and altogether uncooperative. None of her four sons showed any sign of trouble with the skin. Her skin was better during pregnancy and always worse during summer.

CASE 5.—Mrs. W., aged 34, had typical Darier's disease, with characteristic pigmented papular lesions on the neck, trunk and limbs, most clearly marked below the knees. This patient said that her skin also became better during pregnancy, but, in contradistinction to the disease in case 4, it improved in summer and after exposure to sunlight. Her general health is good. None of her children or other members of her family have any trouble with their skin.

CASE 6.—Miss P., aged 19, when first seen had the characteristic firm, pinhead-sized to pea-sized, brownish papules on the neck, legs and arms, but none were present on the trunk. There were wartlike lesions on the backs of the hands, and papules were visible on the palate. An eruption of bright red, discrete papules was present on the chest, having appeared there only three weeks previously. Her position in the family is shown in figure 3.

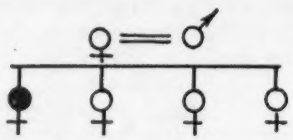

Fig. 3 (case 6).—The familial position of Miss P. is shown by the black disk.

This case is the only one in which improvement has been great, including regression of the warty lesions on the backs of the hands. This patient, it should be noted, is also the only one treated within one year of the development of trouble with the skin. After seven months' treatment only three pigmented papules could be found; these are on the right temple.

CASE 7.—Miss D. was 13 years old. Her family tree is shown in figure 4, no other members of the family being affected. Pigmented papules were numerous

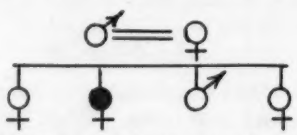

Fig. 4 (case 7).—The familial relationship of Miss D. The patient is indicated by the black disk.

and well marked on the neck, shoulders and limbs, the backs of the hands showing the usual wartlike lesions. Papules were present on both hard and soft palates.

The table shows that of 7 cases, great improvement with vitamin A therapy occurred in 1, much in another, slight in 3 and none at all in 2. Of the 2 patients who did not improve, 1 continued treatment for one month only (case 4), probably too short a time for benefit to appear. The other (case 5) persisted with treatment for three months, when she had taken 9,000,000 international units of vitamin A without result.

It was possible to estimate the vitamin A and carotene levels in the plasma in 4 cases before treatment was begun. The figures were all within normal limits. Dark adaptation tests carried out in 5 cases before any vitamin A was administered all gave curves somewhat outside the normal range.

TREATMENT

Big doses of vitamin A, in the neighborhood of 100,000 units daily, seem to produce the best results, and it is suggested that they should be continued until improvement ceases. With such quantities there appears to be no danger of ill effects from overdosage; 1 of our patients (case 3),

Results of Vitamin A Therapy in Seven Cases of Darier's Disease

			Before Vitamin A Therapy						After Vitamin A Therapy			
Case	Age, Yr.	Sex	Duration of Eruption	Plasma Vitamin A, International Units/ 100 Cc.	Plasma Carotene, Mg./ 100 Cc.	Result of Dark Adaptation Test *	Total Vitamin A, International Units	Duration of Treatment, Mo.	Plasma Vitamin A, International Units/ 100 Cc.	Plasma Carotene, Mg./ 100 Cc.	Dark Adaptation Test, Average Improvement Over Range Tested	Clinical Result
1	33	M	Since childhood	..	..	Subnormal	3,000,000	3	...	..	0.1 log unit	Much improvement
2	30	F	Lifelong	..	..	.....	25,600,000	30	112	44	.....	Slight improvement
3	9	F	6 yr.	..	..	Subnormal	30,000,000	10	308	69	0.1 log unit	Slight improvement
4	42	F	Many years	69	87	.....	900,000	1	...	..	.....	No improvement
5	34	F	3 yr.	134	81	Slightly subnormal	9,200,000	3	124	90	0.1 log unit	No improvement
6	19	F	1 yr.	52	..	Slightly subnormal	21,000,000	7	106	46	Negligible (<0.05 log unit)	Great improvement
7	13	F	8 yr.	87	85	Slightly subnormal	12,000,000	4	122	75	0.2 log unit	Slight improvement

* Dark adaptation test and normal values as described by Yudkin (1941) using a Crookes D.A.T. Range of brightness values of test object used were from 6.0 millimicrons 1 log units to final threshold values (average approximately 3.5 millimicrons 1 log unit).

a child of 9 years, took 100,000 international units daily for ten months, without any sign of toxic symptoms.

The treatment should be continued for at least two months. This is necessary because some patients respond to vitamin A slowly and their conditions might be considered hopeless if treatment were abandoned too early. Once maximum benefit has been achieved it appears that the dose may be reduced to 30,000 units daily.

Since it had been shown by Mandelbaum and Schlessinger (1942) [3] that vitamin A can be absorbed through unbroken skin, an ointment containing 5,000 international units of vitamin A per gram was rubbed into a badly affected area on the patient in case 4 for one month. It was hoped that the possibility of high concentration of the vitamin A in the skin produced by inunction might have a good result, but this was not found to be so, as no beneficial effect was noted.

COMMENT

That vitamin A therapy has beneficial, sometimes even striking, effects in cases of Darier's dyskeratosis can hardly be doubted. The role of vitamin A, however, in Darier's disease is still under discussion. Apart from our own cases, improvement after vitamin A therapy has been recorded by Peck, Chargin and Sobotka (1941) [2] in 4 cases; Barwasser (1941) [4] in 1 case; Cannon (1941) [5] in 1 case; Sweitzer (1942) [6] in 1 case; Michelson (1942) [7] in 1 case; Abramowitz (1942) [8] in 1 case; Peck, Glick, Sobotka and Chargin (1943) [9] in 9 out of 10 cases (4 of which were reported by Peck, Chargin and Sobotka in 1941); Newman (1943) [10] in 1 case; Carleton and Steven (1943) [11] in 2 out of 4 cases,

3. Mandelbaum, J., and Schlessinger, L.: Absorption of Vitamin A Through Human Skin, Arch. Dermat. & Syph. **46**:431 (Sept.) 1942.

4. Barwasser, N. C.: Keratosis Follicularis (Darier) Treated with Vitamin A, Arch. Dermat. & Syph. **44**:961 (Nov.) 1941.

5. Cannon, A. B.: Keratosis Follicularis, Arch. Dermat. & Syph. **44**:1163 (Dec.) 1941.

6. Sweitzer, S. E.: Keratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **45**:628 (March) 1942.

7. Michelson, H. E.: Keratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **45**:628 (March) 1942.

8. Abramowitz, E. W.: Darier's Disease, Arch. Dermat. & Syph. **45**:976 (May) 1942.

9. Peck, S. M.; Glick, A. W.; Sobotka, H., and Chargin, L.: Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **48**:17 (July) 1943.

10. Newman, B. A.: Keratosis Follicularis (Darier) After Treatment with Vitamin A, Arch. Dermat. & Syph. **47**:288 and 293 (Feb.) 1943.

11. Carleton, A., and Steven, D.: Keratosis Follicularis: A Study of Four Cases, Arch. Dermat. & Syph. **48**:143 (Aug.) 1943.

and Leitner (1945) [12] and Leitner and Moore (1946) [13] in 1 out of 6 cases. Nevertheless, in spite of improvement following treatment with vitamin A in so many cases, it is clear that the disease is not a simple deficiency state; if it were, then deficiency, whether occurring naturally or experimentally, would reproduce the disease and treatment with adequate quantities of vitamin A would cure it. Laboratory tests might also be expected to produce evidence of deficiency. None of these three conditions is fulfilled, however. The state of the skin in naturally occurring deficiency, described by Loewenthal (1935),[14] Reiss (1936),[15] Frazier and Hu (1936) [16] and others, differs from that found in Darier's dyskeratosis. This is also true of experimentally produced deficiency, as recorded by Steffens, Bair and Sheard (1939).[17] Moreover, vitamin A, when given in large amounts and over long periods, seldom causes the cutaneous manifestations of Darier's disease to disappear entirely. So far as we are aware, the only patients reported as having recovered completely are the 2 in the cases described by Carleton and Steven (1943),[11] in which there was "complete involution with vitamin A therapy," and a case reported by Newman (1943).[10]

It must be remembered in estimating the effect of any form of treatment that the skin in Darier's dyskeratosis varies considerably from time to time, even when no treatment of any kind is being given. For instance, the patients in cases 3 and 4 both affirm that their skin is invariably worse in summer and that bright sunlight always has an adverse effect. Likewise, Swartz (1942) [18] and Hitch, Callaway and Moseley (1941) [19] mentioned that their patients got worse in summer, the latter

12. Leitner, Z. A., (*a*) in discussion on Stannus, H. C.: Vitamin A and the Skin, Proc. Roy. Soc. Med. **38**:337 (May) 1945; Brit. J. Dermat. **57**:209 (Nov.-Dec.) 1945; (*b*) Three Cases of Dyskeratosis Follicularis and Two Cases of Pityriasis Rubra Pilaris, ibid. **58**:11 (Jan.-Feb.) 1946.

13. Leitner, Z. A., and Moore, T.: Vitamin A in Darier's Disease, Brit. J. Dermat., to be published.

14. Loewenthal, L. J. A.: The Manifestations of Vitamin A Deficiency in Man, Ann. Trop. Med. **29**:407 (Dec.) 1935.

15. Reiss, F.: Contribution to Cutaneous Manifestations of Vitamin A Deficiency, Chinese M. J. **50**:945 (July) 1936.

16. Frazier, C. N., and Hu, C. K.: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency: A Study of Two Hundred and Seven Cases, Arch. Dermat. & Syph. **33**:825 (May) 1936.

17. Steffens, L. F.; Bair, H. L., and Sheard, C.: Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, Proc. Staff Meet., Mayo Clin. **14**:698 (Nov. 1) 1939.

18. Swartz, J. H.: Darier's Disease (Keratosis Follicularis), Arch. Dermat. & Syph. **45**:417 (Feb.) 1942.

19. Hitch, J. M.; Callaway, J. L., and Moseley, V.: Familial Darier's Disease (Keratosis Follicularis), South. M. J. **34**:578 (June) 1941.

calling special attention to the fact that the lesions were practically invisible during the winter. This is rather surprising, for relapses might be expected to occur when the vitamin A content of the diet is at its lowest, during the winter months, and indeed it is at this time that the symptoms of naturally occurring dietary deficiency have been found to be commonest. Again, the patients in cases 4 and 5 insisted that pregnancy was always accompanied with noted improvement in the condition of the skin. Hitch, Callaway and Moseley [19] reported that in their cases the skin became worse during menstruation.

Laboratory methods used to detect deficiency and to estimate the state of vitamin A nutrition are of two kinds: Firstly, the vitamin A and carotene levels in the plasma may be calculated, and, secondly, dark adaptation tests may be carried out.

Estimation of the vitamin A content in the blood has yielded conflicting results. For example, Peck, Glick, Sobotka and Chargin (1943) [9] found the plasma vitamin A level to be subnormal in 8 out of 10 cases and at the lower level of normal in the remaining 2. Moore (1946) [20] found the mean average level to be within normal limits in 3 cases, though individual estimation revealed subnormal levels in 2 of them on certain occasions. Carleton and Steven (1943),[11] however, reported normal levels in all their 4 cases, and Cornbleet, Popper and Steigmann (1944) [21] mentioned finding a normal level of plasma vitamin A in the only patient with Darier's dyskeratosis examined. In our own series the figures were within normal limits in all, including the 4 cases in which estimations were made before vitamin A therapy was begun. It must be remembered that determination of the plasma vitamin A content as a means of estimating the state of vitamin A nutrition is open to criticism (Carleton and Steven, 1943,[11] and Porter and Godding, 1945 [22]).

A subnormal curve found by dark adaptation tests can provide satisfactory evidence of vitamin A deficiency only if the curve improves under vitamin A therapy. Of the 4 cases in our series in which dark adaptation tests were performed, the original curves (before vitamin A therapy was begun) were all outside the normal range as determined by Yudkin (1941).[23] After treatment there was a small but general tendency to improvement, the extent being indicated in the table; it will be seen,

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20. Moore, T.: Plasma Vitamin A in Keratosis Follicularis and Pityriasis Rubra Pilaris, Brit. J. Dermat. **58**:17 (Jan.-Feb.) 1946.

21. Cornbleet, T.; Popper, H., and Steigmann, F.: Blood Vitamin A and Cutaneous Diseases, Arch. Dermat. & Syph. **49**:103 (Feb.) 1944.

22. Porter, A., and Godding, E. W.: (*a*) Dark Adaptation Studies in Patients with Diseases of the Skin, Brit. M. J. **1**:840 (June 16) 1945; (*b*) Pityriasis Rubra Pilaris and Vitamin A, Brit. J. Dermat. **57**:197 (Nov.-Dec.) 1945.

23. Yudkin, S.: A New Dark Adaptation Tester, Brit. J. Ophth. **25**:231 (May) 1941.

however, that the observations on the dark adaptation tests could not be correlated with the clinical picture in all cases.

The conditions, then, required to show that Darier's dyskeratosis is caused solely by deficiency of vitamin A are not fulfilled, and it becomes necessary to find another hypothesis. The one which seems to us to fit the facts most satisfactorily is that the epithelial cells of the skin are unable to make use of the vitamin A available in a normal manner. This idea is consistent with the common finding of normal amounts of vitamin A in the plasma, as mentioned previously. It may also possibly explain why in cases in which both estimation of plasma levels and dark adaptation tests were carried out before vitamin A was given the curves were subnormal in each case though the plasma vitamin A level was normal. Such results suggest either that the synthesis of vitamin A–containing substances (e. g., photochemical pigments) is defective or that there is some interference with the normal use of such substances by the tissues concerned (Wise and Sulzberger, 1941, and Sulzberger and Baer, 1943 [24]).

Attempts to explain the pathogenesis of Darier's disease on a histologic basis have been made by Brunauer (1925) [25] and Goodman and Pels (1939, 1941).[26] It has been shown by these authors that the fundamental changes in Darier's dyskeratosis are multiplication of the basal cells with downward prolongations and absence of prickles. The cells do not adhere one to another in the usual way; lymph collects between them, and lacunas and fissures appear. Keratinization does not take place in a normal manner; instead, affected cells undergo degenerative changes and form either "grains" or *corps ronds*. Not only is the primary function of keratinization grossly disturbed, but another function of the basal cells—the formation of pigment—is also seriously affected (Mu, 1930).[25] Thus the development of these cells is so disorganized that two of their most important functions, keratinization and pigment formation, do not take place in a normal manner. It is suggested that another function of the basal cells is more or less upset in Darier's disease, that is, the ability to utilize vitamin A or its derivatives in a normal manner or to synthesize vitamin A–containing compounds as required. It is

24. (*a*) Wise, F., and Sulzberger, M. B.: The 1941 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1942, p. 450. (*b*) Sulzberger, M. B., and Baer, R. L.: The 1943 Year Book of Dermatology and Syphilology, ibid., 1944, p. 199.

25. Brunauer, S. R., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 210.

26. (*a*) Goodman, M. H., and Pels, I. R.: Bullous Dyskeratosis of the Keratosis Follicularis (Darier) Type, Arch. Dermat. & Syph. **44**:359 (Sept.) 1941. (*b*) Pels, I. R., and Goodman, M. H.: Criteria for the Histologic Diagnosis of Keratosis Follicularis (Darier): Report of a Case with Vesiculation, ibid. **39**:438 (March) 1939.

thought that this failure explains why large doses of vitamin A are required to produce the beneficial results which occur in many cases from treatment with vitamin A.

Whatever the defect may be, it appears to be inherited. Bettmann (1921) [25] called it "a specific or peculiar, inborn property of the skin in Darier's disease which responds to trauma of all kinds in a way specifically characteristic of this disease." The nature of the inheritance, however, is still under discussion. According to F. Fischer (1925) [25] it is a highly irregular dominant, whereas Cockayne (1933),[27] after reviewing the family histories in more than 200 cases, suggested that, as far as the familial cases are concerned, the defect is a simple dominant and that in isolated cases "the abnormality arose in each case de novo by mutation." It is because of this difference of opinions that we give details of siblings in the notes on the cases.

The foregoing explanation of the sometimes beneficial effect of vitamin A in cases of Darier's dyskeratosis is based on the histologic changes of the disease. It is as yet uncertain whether these changes are associated with impairment of hepatic function or abnormalities in the balance of vitamin A between the hepatic reserves and blood plasma, as suggested by Leitner and Moore (1946).[13] This question requires further investigation.

One fact is, however, perhaps worth mentioning. Apart from phrynoderma—the naturally or experimentally occurring deficiency which can be cured by adequate dosage—vitamin A has been tried in numerous cutaneous diseases, particularly in Darier's disease, in pityriasis rubra pilaris (Gross, 1941 [28]; Brunsting and Sheard, 1941 [29]; Weiner and Levin, 1943 [30]; Porter and Godding, 1945,[22] and Leitner, 1945 [12]) and in ichthyosis (Peck, Glick and Chargin, 1943 [31]). In Darier's dyskeratosis and in pityriasis rubra pilaris the effect is sometimes good. In contrast to this is the response in 2 cases of ichthyosis reported by Peck, Glick and Chargin (1943).[31] In both, the plasma vitamin A content was greatly below normal and dark adaptation tests gave subnormal values; yet no improvement was produced by vitamin A even when the vitamin blood levels were brought back to normal and maintained so for

27. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933.

28. Gross, P.: Pityriasis Rubra Pilaris and Vitamin Therapy, Arch. Dermat. & Syph. **44**:270 (Aug.) 1941.

29. Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42 (Jan.) 1941.

30. Weiner, A. L., and Levin, A. A.: Pityriasis Rubra Pilaris of Familial Type: Experience in Therapy with Carotene and Vitamin A, Arch. Dermat. & Syph. **48**:288 (Sept.) 1943.

31. Peck, S. M.; Glick, A. W., and Chargin, L.: Vitamin A Studies in Cases of Ichthyosis, Arch. Dermat. & Syph. **48**:32 (July) 1943.

a long time. In ichthyosis there are no major changes in the basal cells resembling those which occur more or less regularly in Darier's disease and to a lesser degree in pityriasis rubra pilaris. Havas, quoted by Juliusberg (1931),[32] reported increase in number of the basal cells and loss of prickles in pityriasis rubra pilaris. It seems to be no mere coincidence that in Darier's dyskeratosis and pityriasis rubra pilaris, the two diseases which have certain histologic features in common, response to vitamin A therapy is sometimes excellent whereas in the aforementioned cases of ichthyosis, in which the histologic structure is totally different, no benefit from treatment with vitamin A was obtained.

The term "keratosis follicularis" has been avoided throughout this paper because it is doubtful whether the keratosis occurring in Darier's disease is principally one of the follicles (Darier, 1889[1]; Brunauer, 1931,[25] and Ellis, 1944[33]). It is for this reason that we prefer the synonyms "Darier's disease" and "Darier's dyskeratosis."

SUMMARY

The vitamin A and carotene levels in the plasma were within normal limits in 4 cases of Darier's disease in which estimations were made before treatment was begun.

Dark adaptation tests carried out before vitamin A was given in 4 cases revealed curves somewhat outside the normal range in all, with improvement under treatment in 3, although close correlation with the clinical picture was not established.

Of 7 cases, great clinical improvement with vitamin A therapy occurred in 1, much in another, but little in 3 and none in 2.

It is suggested that doses of about 100,000 units of vitamin A should be given daily and continued until improvement ceases, when smaller doses may be instituted. Treatment should not be abandoned under two months at least.

No benefit was obtained from inunction of an ointment containing 5,000 international units of vitamin A per gram.

The histopathologic changes of Darier's disease show as fundamental features hyperplasia of the basal cells of the epidermis and loss of prickles. As a consequence of these changes, fissures and lacunas, *corps ronds* and "grains" appear and the primary functions of the basal cells, keratinization and pigment formation, are grossly disturbed. It is suggested that another function of the basal cells is more or less upset in Darier's disease, namely, the ability to utilize vitamin A or its derivatives in a normal manner or to synthesize vitamin A–containing com-

32. Juliusberg, F.: Pityriasis rubra pilaris, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 144.

33. Ellis, F. A.: Keratosis Follicularis Is Not Primarily a Follicular Disease, Arch. Dermat. & Syph. **50**:27 (July) 1944.

pounds as required. This failure may explain why large doses of vitamin A are required to produce the beneficial effect which occurs in many cases from treatment with vitamin A.

We believe that support is given to this hypothesis by the good results of treatment with vitamin A in pityriasis rubra pilaris, a disease in which the histologic picture resembles in certain respects that seen in Darier's disease.

The fact that in 2 cases of ichthyosis in which evidence of vitamin A deficiency was reported by Peck, Glick and Chargin no benefit was obtained by vitamin A therapy seems to favor the foregoing hypothesis.

Prof J. R. Marrack, M.D., D.S.O., M.C., estimated the levels of vitamin A in the plasma in all cases; Dr. Sydney Thompson and Dr. H. Corsi referred cases to us for investigation, and Messrs. Crookes Laboratories, Ltd., loaned the apparatus for dark adaptation tests and generously supplied vitamin A.

TREATMENT OF CUTANEOUS TUBERCULOSIS WITH LARGE DOSES OF VITAMIN D_2

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DURING the last two years numerous reports have appeared in the European literature concerning the use of vitamin D in the treatment of cutaneous tuberculosis. Investigators in Belgium, France and England independently investigated the oral administration of large doses of vitamin D_2.

In the years which followed the announcement by Steenbock and his colleagues [1] of an antirachitic substance in irradiated sterols, Malmström, Villaret, Justin-Besançon and Fauvert, Bergmann [2] and others discovered that these new forms of vitamin D were useful in the treatment of various types of tuberculosis.

In 1930 Levaditi and Po and Spies [3] reported that experimental tuberculosis in rabbits was distinctly benefited by the administration of large doses of irradiated ergosterol. These investigators observed that tuberculous tissue had a selective tendency to become calcified under the influence of this substance. A mineral shell formed around the areas of necrosis, and within this shell the tubercle bacilli were observed to be

From the Division of Dermatology of the University of Minnesota, Dr. Henry E. Michelson, Director.

1. Steenbock, H.; Nelson, M. T., and Black, A.: Determinations of Vitamin A, J. Biol. Chem. **59**:ix (Feb.) 1924. Steenbock, H., and Black, A: Fat Soluble Vitamins: The Induction of Growth-Promoting and Calcifying Properties in a Ration by Exposure to Ultra-Violet Light, ibid. **61**:405 (Sept.) 1924.

2. (*a*) Malmström, V.: Investigations Concerning the Influence of Light on Fat and Kindred Substances: Therapeutical Experiments with a Preparation Produced from Irradiated Cod-Liver-Oil, Acta radiol. **4**:173, 1925. (*b*) Villaret, M.; Justin-Besançon, L., and Fauvert, R.: Actinothérapie indirecte de la tuberculose, Presse méd. **34**:753 (June 16) 1926. (*c*) Bergmann, G. V.: Rachitis- und Tuberkulosebehandlung, Deutsche med. Wchnschr. **55**:1407 (Aug. 23) 1929.

3. (*a*) Levaditi, C., and Li, Y. P.: Étude expérimentale de la calcification des lésions tuberculeuses sous l'influence de l'ergostéral irradié, Presse méd. **38**: 168 (Feb. 5); 1720 (Dec. 17) 1930. (*b*) Spies, T. D.: The Calcification of Tubercles by Means of Irradiated Ergosterol, Am. J. Path. **6**:337 (May) 1930.

deformed and poorly stained. Levaditi and Po suggested that irradiated ergosterol was worthy of trial in the treatment of human tuberculosis.

Fanielle [4] followed this line of investigation, using irradiated ergosterol in the treatment of human tuberculosis and after twelve years of observations concluded that it was of distinct value. During the later years of his observations he used 15 mg. of vitamin D_2 daily for fifteen days along with calcium gluconate. Under this regimen he reported favorable results in 4 cases of lupus vulgaris, 2 cases of ulcerated tuberculosis and 1 case of verrucous cutaneous tuberculosis. Alechinsky [5] confirmed these observations and reported the cure in several cases by the same method.

In 1943 and 1944 Charpy [6] reported 39 cases of lupus vulgaris in which treatment was by the same method except that vitamin D was administered in an alcoholic solution, less frequently and over a longer period. Cures were obtained in each instance, although in 27 cases some form of local destructive therapy was used in addition to the vitamin and calcium. According to Charpy the results were rapid and dramatic, and the beneficial effect, greatest during the initial period, continued for four or five months. The mucosal lesions, lymphangitis and adenitis were quickly reduced, but the cutaneous nodules were more resistant and often required cauterization.

Adopting the method which was described by Charpy, Gougerot and Gaullier [7] obtained cures in about 60 per cent of 32 patients with lupus vulgaris. Huriez and Leborgne [8] reported 4 failures out of 15 cases of lupus vulgaris and satisfactory results in 2 cases of lichen scrofulosus and 1 case each of tuberculous gumma and erythema induratum. Garric [9] obtained remarkable results in 10 cases of lupus vulgaris in which treatment was by Charpy's method. In 2 cases of particularly severe lupus vulgaris rapid cure was obtained by the intramuscular

4. Fanielle, M. G.: Le traitement des affections d'origine tuberculeuse par l'ergosterol irradié associé a la calcithérapie, Scalpel **95**:539 (Dec.) 1942.

5. Alechinsky, A.: La méthode de Fanielle dans le traitement des tuberculoses cutanées, Bruxelles-méd. **25**:838 (Sept. 23) 1945.

6. Charpy, M. J.: Technique de traitement du lupus tuberculeux, Ann. de dermat. et syph. **3**:331 (Nov.-Dec.) 1943; Les reactions tuberculiniques apres traitement des lupus tuberculeux, ibid. **4**:110 (March-April) 1944; Le traitement des lupus tuberculeaux et tuberculoses cutanées par la vitamine D, Bull. Acad. de méd., Paris **108**:498 (Oct.) 1944.

7. Gougerot, H., and Gaullier: Traitement de Charpy dans les tuberculoses cutanées, Ann. de dermat. et. syph. **4**:210 (July-Aug.) 1944.

8. Huriez, C., and Leborgne, J.: Action de la vitamine D a doses massives dans le traitement des tuberculoses cutanées, Ann. de dermat. et syph. **4**:211 (July-Aug.) 1944.

9. Garric, M.: Apropos de traitement du lupus tuberculeux par la méthode de Charpy, Ann. de dermat. et syph. **4**:313 (Nov.-Dec.) 1944.

injection of vitamin D ("sterogyl") in oil. Bureau and Barrière [10] treated 26 patients with cutaneous tuberculosis by the same method and were able to cure all but 1 (a case of papulonecrotic tuberculid which seemed to be made worse by the therapy). Vachon [11] treated 29 patients with only 1 failure, although he resorted to local therapy to complete the cure in most cases. Michel and Pellerat [12] also reported favorably on the method.

From the Finsen Institute, Meyer, Gaulier and Desgrez [13] reported the treatment of over 300 patients by Charpy's method. Good results were obtained in about 75 per cent, but a high incidence of recurrence was reported.

Dowling and Thomas [14] treated 38 patients with lupus vulgaris by oral administration of 150,000 units of calciferol (vitamin D_2) daily. The results of treatment were assessed in 32 patients, 18 of whom appeared to be cured and 9 considerably improved.

A recent issue of the *Annales de dermatologie et de syphiligraphie* [15] contained a symposium on this subject with a complete bibliography.

RÉSUMÉ OF CASES

We have administered vitamin D to 6 patients with cutaneous tuberculosis. They have been under observation for periods varying from two to five months. The small number of patients and the short period of observation make this no more than a preliminary report. Two patients with lupus vulgaris, 1 with tuberculosis colliquativa and

10. Bureau, Y., and Barrière: Résultats obtenus par la vitamine D_3 (méthode de Charpy) dans le traitement de la tuberculose cutanée et de certaines dermatoses, Ann. de dermat. et syph. **5**:196 (July-Aug.) 1945.

11. Vachon, R.: Le traitement du lupus tuberculeux par la méthode de Charpy, Ann. de dermat. et syph. **6**:91 (Feb.) 1946.

12. Michel, P. J., and Pellerat, J.: Resultats eloignes de la méthode de Charpy pour de traitement des lupus, Ann. de dermat. et syph. **4**:114 (March-April) 1944.

13. Meyer, J.; Gaulier, and Desgrez: La vitamine—calcithérapie dans le traitement due lupus au laboratoire du Finsen, Ann. de dermat. et syph. **6**:348 (May) 1946.

14. Dowling, G. G., and Thomas, E. W. P.: Treatment of Lupus Vulgaris with Calciferol, Brit. J. Dermat. **58**:45 (March-April) 1946.

15. Charpy, M. J.: Le traitement des tuberculoses cutanées par la vitamine D_3 à hautes doses, Ann. de dermat. et syph. **6**:310 (May-June) 1946. Fanielle, M. G.: Entretien sur la question de priorité, ibid. **6**:346 (May-June) 1946; Toxicité de la méthode, ibid. **6**:347 (May-June) 1946. Meyer, J.; Gaulier, and Desgrez: La vitamine-calcithérapie dans le traitement du lupus au laboratoire du Finsen, ibid. **6**:348 (May-June) 1946. Lapière, S.: Résultats du traitement du lupus vulgaire par les vitamines D à hautes doses, ibid. **6**:350 (May-June) 1946. Lefevre, P., and Hallé, G.: 35 cas de lupus tuberculeux traités par la vitamine D_3 à haute dose (traitement de Charpy): Remarquables resultats, ibid. **6**:355 (May-June) 1946. Levaditi, M. C.: Action calcifiante de la vitamine D sur les lésions tuberculeuses expérimentales, ibid. **6**:356 (May-June) 1946.

3 with erythema induratum were included in the study. All, with the exception of 1 case of tuberculosis colliquativa, were old cases which had resisted previous therapy. The results were less dramatic than had been expected from a study of the French reports, but each patient has shown an initial and progressive improvement. None are as yet cured.

As the alcoholic solution which was recommended by Charpy was not commercially available in the United States, viosterol in oil was used in a dosage of 150,000 international units daily. An adequate intake of calcium was assured by having the patients drink at least 1 quart (946 cc.) of milk daily.

TOXIC REACTIONS

Most drugs, including vitamin D, have a limit of dosage which if exceeded results in toxic and occasionally fatal reactions. The extreme toxicity of viosterol as described in the older reports was probably due to the presence of an excess of toxisterol.[16] In human beings and with modern methods of preparation, the incidence of intoxication is relatively low, and the toxic dose is about 20,000 international units per kilogram of body weight per day.[17] This is from five to ten times greater than the doses that were employed in the present study. The kidneys and the aorta are parts of the body which are most vulnerable to excessive doses, and, according to some, renal disease and arteriosclerosis constitute contraindications to such therapy.

Thatcher [18] called attention to the possibility, especially in infants, of an idiosyncrasy to viosterol and reported a case in which this intolerance may have been the cause of death.

For the most part, administration of vitamin D in the doses which are recommended is perfectly safe, and the French authors comment on the lack of reactions. Dowling and Thomas [14] noted signs of intolerance in 8 out of 38 patients (mild in all but 1), all of whom were able to tolerate smaller doses without discomfort.

In 1 patient who was observed by us, anorexia and loss of weight occurred but were of such mild degree that we were able to continue treatment with full dosage.

The symptoms of overdosage as listed by Bills [16] are: nausea and loss of appetite, vomiting, cramps, diarrhea and frequent urination, occasionally neuralgia along the course of the mandibular nerve, tenderness of the gums and teeth, muscular and articular pains, dizziness,

16. Bills, C. E.: Physiology of the Sterols, Including Vitamin D, Physiol. Rev. **15**:1 (Jan.) 1935.

17. Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. C.: Further Studies on Intoxication with Vitamin D, Ann. Int. Med. **10**:951 (Jan.) 1937.

18. Thatcher, L.: Hypervitaminosis D, Lancet **1**:20 (Jan. 4) 1936.

muscular weakness, headache, haziness of memory and numbness and tingling of the extremities.

The subjective symptoms are considered the most valuable index of tolerance or intolerance of therapy with large doses of vitamin D. The concomitant administration of calcium and phosphorus and exposure to solar or ultraviolet rays augment the effect of vitamin D and may thus render it more toxic.

COMMENT

Vitamin D in the form of cod liver oil has been one of the valuable adjuncts to the treatment of cutaneous tuberculosis for over a hundred years. In 1848 Emery [19] treated 74 patients with lupus vulgaris by administering cod liver oil. He employed up to one quart a day (100,000 units of vitamin D), but, although the results were excellent, the unpalatability of such large amounts of cod liver oil made the method impracticable.

The beneficial effects of generalized ultraviolet irradiation as employed in the treatment of lupus vulgaris by Heiberg and With and by Sequeira [20] may depend for their action on the conversion of the sterols in the skin into vitamin D or associated products.

Charpy insisted that the alcoholic solution of vitamin D_2 was more effective than a solution in oil. Both are good solvents for this vitamin, and neither oil nor alcohol is believed to produce any physical or chemical change in the vitamin. There is some indication that, unit for unit, the concentrated solutions have less antirachitic activity, and it may be that the alcoholic solution is more active because of its miscibility with the gastric contents. Unless dispensed in ampule form the volatility of the alcoholic solution would produce a concentration of the drug with resulting inaccuracy in dosage. Recently we have changed to a solution of vitamin D_2 in propylene glycol [21] which was especially prepared for us in a form containing 50,000 units per cubic centimeter. As propylene glycol is readily miscible with the gastric contents, it is felt that more beneficial results might be obtained with this vehicle.

Most of the French authors, including Charpy, administered calcium in addition to the vitamin. Dowling and Thomas [14] omitted calcium. We do not consider this supplementary calcium necessary if an adequate amount is contained in the diet (i. e., 1 quart of milk daily).

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19. Emery, M.: Sur l'emploi de l'huile de foie de morue a haute dose dans le traitement du lupus, Bull. gén. de thérap. méd. et chir. **35**:373, 1848.

20. Heiberg, K. A., and With, C.: Lupus Treated with General Carbon Arc-Light Baths as the Only Therapy, Brit. J. Dermat. **34**:69 (March) 1922. Sequeira, J. H.: Carbon-Arc Light Baths in the Treatment of Lupus Vulgaris, ibid. **35**:93 (March) 1923.

21. This preparation ("drisdol") was furnished by the Winthrop Chemical Company.

The means by which irradiated ergosterol (vitamin D_2) exerts a beneficial influence on cutaneous tuberculosis is not definitely known. Large doses may have an action quite different from the physiologic effects of small antirachitic doses. The substance may be acting as a drug rather than as a vitamin, as the sterols themselves have a detoxifying action against numerous hemolytic agents, venoms and bacterial toxins.[16] Levaditi and Li [3] observed that tuberculous tissue in animals had a selective affinity for calcification and that the administration of large doses of irradiated ergosterol aided this process. They expressed the opinion that this calcification interfered with the propagation of the tubercle bacilli and prevented their spread to adjacent areas. If the beneficial effect of irradiated ergosterol is due entirely to such selective calcification, it is possible that tachysterol, which is present in irradiated ergosterol and which has no antirachitic activity, may be the substance which is responsible for the therapeutic effect.

The method of Charpy produced remarkable clinical results in lupus vulgaris according to Vachon and Feroldi,[22] but histologic evidence of cure was not always obtained. In most cases they observed a progressive cicatricial smothering of the lesions with disappearance of the active inflammatory elements. They stated the belief that the improvement was not due to actual calcification of the lesions.

Crimm and Strayer [23] expressed the belief that the administration of large doses of viosterol to patients with pulmonary tuberculosis was attended by more rapid clearing and fibrosis in some cases. They concluded that this was the result of an increase in the nondiffusible calcium which was produced by the hypervitaminosis. Gelfan [24] showed that the consumption of oxygen of an isolated tissue (frog muscle) was increased during the administration of viosterol. Reed, Thacker, Dillman and Welch [25] observed that the administration of large doses of vitamin D increased the metabolic rate, and if continued a cellular injury and later a deposit of calcium in the injured cells resulted.

In lupus vulgaris there exists a delicate but fixed balance between the invading organism and the bodily resistance, neither being able to advance or retreat except over periods of months or years. Healing does

22. Vachon, R., and Feroldi, J.: Le traitement du lupus tuberculeux par la méthode de Charpy: Les résultats anatomiques, Ann. de dermat. et syph. **5**:241 (Sept.-Oct.) 1945.

23. Crimm, P. D., and Strayer, J. W.: Vitamin Therapy in Pulmonary Tuberculosis, Am. J. M. Sc. **187**:557 (April) 1934. Crimm, P. D.: Vitamin Therapy in Pulmonary Tuberculosis, Am. Rev. Tuberc. **26**:112 (Aug.) 1932.

24. Gelfan, S.: The Effect of Viosterol upon the Oxygen Consumption of Frog's Muscle, Am. J. Physiol. **113**:464 (Oct.) 1935.

25. Reed, C. I.; Thacker, E. A.; Dillman, L. M., and Welch, J. W.: The Effect of Irradiated Ergosterol on the Metabolism of Normal Dogs, J. Nutrition **6**:355 (July) 1933.

not occur by simple absorption, as in syphilis or sarcoidosis, but only by fibrosis and scarring. It seems logical, therefore, that a therapeutic agent which at first increases cellular metabolism and then produces cellular injury and calcification might favorably influence this existing equilibrium in favor of the scarring fibrotic type of healing which is so characteristic of lupus vulgaris. The selective affinity of tuberculous tissue for calcification was previously mentioned and seems important in explaining why normal tissues are not damaged with the employed dosage.

If in the future a deficiency of vitamin D or associated sterols is observed to have a bearing on the cause of cutaneous tuberculosis, some interesting facts may thereby be explained, such as the excessive incidence of the disease in northern European countries where the population is often subjected to diets which are deficient in vitamin D, phosphorus and calcium.[26] In other sections where this deficiency exists, an abundance of sunshine would offset the deficiency in diet. In all countries, however, there are a few persons who are unable to utilize vitamin D and calcium, as demonstrated by the occurrence of refractory rickets.

The onset of lupus vulgaris in childhood could also be explained in part by the increased requirement of the preadolescent for this vitamin as well as by his inability to store it in the body. Follis and his colleagues [27] reported that the postmortem examination of 230 children showed the presence of rickets in 46.5 per cent, whereas the presence of demonstrable vitamin D deficiency in adults is rare.

Many points need clarification before this therapy can be fully accepted. The initial enthusiasm of the French investigators may in time be modified. Our series is not large enough nor has sufficient time elapsed for any conclusions to be drawn other than to state that vitamin D therapy was definitely helpful in each case.

The rarity of the disease in America makes the accumulation of a large or controlled series difficult. We must look to European workers or to animal experimentation for the answer to such questions as (1) the most effective form of the vitamin or sterol (there are at least ten different substances which demonstrate antirachitic activity), (2) the best vehicle for the vitamin and (3) the advisability of administering calcium. In the meantime, the administration of vitamin D to patients with cutaneous tuberculosis in a dosage of 150,000 units daily constitutes, in our opinion, the most useful therapy available.

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26. Hinglais, H., and Hinglais, M.: Remarques sur la carence grave du régime actuel en phosphore, calcium et vitamine D, Presse méd. **49**:694 (June 25-28) 1941.

27. Follis, R. H., Jr.; Jackson, D.; Eliot, M. M., and Park E. A.: Prevalence of Rickets in Children Between Two and Fourteen Years of Age, Am. J. Dis. Child. **66**:1 (July) 1943.

SUMMARY

The literature concerning the use of vitamin D in cutaneous tuberculosis is reviewed.

A modification of the methods suggested by Fanielle and Charpy was used in 6 cases. At the time of this report all patients were considerably benefited, but insufficient time has elapsed to draw any final conclusions.

The use of propylene glycol as a vehicle for viosterol is suggested.

The experimental evidence concerning selective calcification, increased cellular metabolism and injury is reviewed, and a possible explanation is offered for the effect of therapy with massive doses of vitamin D in human tuberculosis.

Medical Arts Building, Minneapolis.

CUTANEOUS REACTIONS TO PENICILLIN

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H. V. ALLINGTON, M.D.
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SINCE penicillin, in the process of its present day manufacture, takes substances from two sources, namely, the fungus Penicillium and the culture medium, which are known to be potential antigens, it would be reasonable to predict that penicillin would be capable of producing the same types of allergic reactions as would these parent substances. This prediction has come true in the experience of users of penicillin. It will be the purpose of this paper to correlate and to describe the various types of cutaneous reactions which have occurred in our practice and that of our colleagues.

CONTACT DERMATITIS

As penicillin in the strengths usually applied to the skin in solutions or in ointments is not a primary cutaneous irritant, it should not, in theory, produce contact dermatitis when applied to skin which has not been sensitized by previous application of penicillin or by some other fungus.

Cohen and Pfaff [1] have reported that 0.95 per cent of normal patients who did not have a history of having used penicillin previously gave positive reactions to patch test with penicillin. If one believes the laws of dermatologic allergy, this would indicate that a small percentage of the general public has been sensitized by some previous fungous infection and can be expected to react when penicillin is first applied to their skin.

Binkley and Brockmole [2] were among the first to report contact dermatitis from penicillin. Their patient, a physician, experienced

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1. Cohen, T. M., and Pfaff, R. O.: Penicillin in Dermatologic Therapy: Report of Results in One Hundred Cases, Arch. Dermat. & Syph. **50**:172-177 (March) 1945.

2. Binkley, G. W., and Brockmole, A.: Dermatitis From Penicillin: Report of Two Cases, Arch. Dermat. & Syph. **50**:326-327 (Nov.) 1944.

contact dermatitis of the face, hands and fingers after handling penicillin solution. His reaction to a patch test with penicillin was positive.

Silvers'[3] patient, a chemist, experienced contact dermatitis of the eyelids and of the penis from handling yellow amorphous sodium penicillin. Reactions to patch tests with this substance were positive, but reactions were negative with pure white crystalline sodium penicillin solution.

Barker[4] reported a similar positive reaction to a patch test in a physician handling penicillin.

Pyle and Rattner[5] in a patch test of a patient, a physician who had contact dermatitis from penicillin noted that the patient reacted negatively to the culture medium, mildly to pure penicillin and to crystalline penicillin and strongly to the whole product. They concluded that the dermatitis was from penicillin itself. Three corpsmen who handled penicillin had pruritus of the face and of the genitals without actual dermatitis.

Siefert[6] reported severe contact dermatitis of the thighs and of the knees from the use of a wet dressing of penicillin in the treatment of secondarily infected tinea cruris. Presumably the tissues had been sensitized by the fungous infection of the groin. Reaction to a patch test was positive.

Pringle[7] said, "I do not have exact figures, but there is approximately a 20 per cent incidence of dermatitis resulting from the local application of penicillin, particularly on the face (when used for sycosis vulgaris or similar diseases). This is irrespective of previous use parenterally, orally or by local application. The percentage of dermatitis is considerably less when used on areas other than the face. The base used (in my experience) does not seem to make any difference. I believe that the brand does make some difference, but because of the process of manufacture of the ointment I have used I have had no real check on this. The dermatitis from penicillin resembles the dermatitis seen in ammoniated mercury sensitivity. I recommend to all patients using the ointment that they employ a patch test for two or three days before applying it to larger areas."

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3. Silvers, S. H.: Contact Dermatitis From Amorphus Sodium Penicillin, Arch. Dermat. & Syph. **50**:328-329 (Nov.) 1944.

4. Barker, A. N.: Allergic Reactions to Penicillin, Lancet **1**:177-178 (Feb. 10) 1945.

5. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 29) 1944.

6. Siefert, H. J.: Personal communication to the authors.

7. Pringle, B.: Personal communication to the authors.

Markson,[8] Bechet [9] and Bedford [10] have reported examples of contact dermatitis from penicillin, patch tests with which also showed positive reactions.

We have seen cases of contact dermatitis from penicillin in our own practice. A physician experienced severe dermatitis of the face when he used a solution containing 500 units of penicillin per cubic centimeter for folliculitis of the beard. Reaction to a patch test was mildly positive. We have had 12 more patients with contact dermatitis from penicillin, all of whom were being treated for various dermatoses. We do not have knowledge of the source of manufacture. In 6 of these patients the dermatitis resulted from the use of penicillin in ointment form. Six patients used penicillin in solution form as continuous wet compresses in dilution of 100,000 units to a pint of water.

CONTACT CHEILITIS, STOMATITIS AND CONJUNCTIVITIS

Goldman [11] reported severe cheilitis in a patient who had used sodium penicillin solution and who had previously used a calcium penicillin ointment for aphthous stomatitis without reaction. Reactions to patch tests with the offending solution were positive but were negative with each of three other brands of sodium penicillin solution and with calcium penicillin ointment. These observations are of practical importance, as they indicate that we may be able to continue needed penicillin therapy in patients who are sensitive to penicillin by changing the brand of penicillin.

Wright and Rule [12] reported mild to severe stomatitis, glossitis or pharyngitis in 16 of 151 patients who were given sodium penicillin lozenges or calcium penicillin lozenges for various dental and oral infections. They do not make mention of patch tests.

Phillips [13] reported 17 instances (up to 18 per cent of his cases) of mild to severe glossitis and stomatitis due to penicillin lozenges and penicillin troches. These contained calcium penicillin, powdered sugar, calcium stearate and acacia. Since all of the ingredients, other than penicillin, are in common use in lozenges the author concluded that calcium penicillin was the irritant.

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8. Markson, L. S.: Dermatitis Venenata Following Use of Penicillin Ointment, Arch. Dermat. & Syph. **52**:384 (Nov.-Dec.) 1945

9. Bechet, P. E.: Induced Sensitivity from the Topical Use of the Sulphonamides and Penicillin, Pennsylvania M. J. **49**:417-420 (Jan.) 1946.

10. Bedford, P. D.: A Case of Penicillin Dermatitis, Brit. M. J. **1**:51-52 (Jan. 12) 1946.

11. Goldman, L.: Cheilitis from Local Use of Penicillin Solutions in the Mouth: Report of Cases, Arch. Dermat. & Syph. **53**:133-134 (Feb.) 1946.

12. Wright, R. B., and Rule, R. W., Jr.: J. California State Dent. A. **21**: 177 (Nov.-Dec.) 1945; **22**:7 (Jan.-Feb.) 1946.

13. Phillips, E.: Glossitis and Stomatitis Due to Penicillin Lozenges and Troches, Permanente Found. M. Bull. **4**:20-23 (Feb.) 1946.

Pringle [7] noted a 10 per cent incidence of stomatitis from the use of troches containing penicillin.

We have seen 2 cases of conjunctivitis and dermatitis of the eyelids after use of eye drops containing penicillin. Several ophthalmologists have reported similar cases to us. Pringle reported a 1 per cent incidence of conjunctivitis and dermatitis of the eyelids among users of drops and ointments for the eye containing penicillin. Benkwith [14] noted positive reactions to intradermal tests and to patch tests in a patient who experienced dermatitis of the eyelids and of the face after instillation of calcium penicillin solution into the conjunctival sacs.

DERMAL TYPES OF REACTIONS

Toxic macular or scarlatiniform eruptions which follow the injection of penicillin are fairly common. They generally occur within the first few days after injections of penicillin, which is earlier than the onset of urticaria after administration of penicillin. We have not seen any of these eruptions progress to generalized exfoliative dermatitis, nor have we heard of any such cases in the practices of our colleagues.

The commonest dermal reaction is urticaria. There have been many reports in literature of its occurrence.[15] Lyons [15b] has reported an incidence of urticaria of 15.7 per cent among 209 patients after injection of penicillin. So many of our colleagues reported examples of urticaria among their patients that we ceased recording the details, as they all followed a rather typical pattern. Urticaria usually occurred on about the seventh, eighth or ninth day after injection of penicillin and varied from a mild form to one with such severe involvement that 1 of our patients threatened suicide. Two of our patients have had severe urticaria associated with nausea, fever and painful swollen joints of the type seen in typical serum sickness. Dr. F. G. Novy Jr. permitted us to see 1 of his patients with this type of severe reaction. Three physicians known to us have suffered from severe urticaria after injections of penicillin. There has not been any uniformity in the type of penicillin injected into these patients with urticaria, various brands, salts and vehicles having been employed.

One patient whom we saw at the Alameda County Hospital had macules, papules and painful nodules of the erythema multiforme–

14. Benkwith, K. B.: Allergy to Penicillin Calcium Topically in Blepharoconjunctivitis, U. S. Nav. M. Bull. **46**:279-280 (Feb.) 1946.

15. (*a*) Macey, H. B., and Hays, T. G.: Allergic Reactions to Penicillin Therapy: Report of Cases, U. S. Nav. M. Bull. **45**:1143-1146 (Dec.) 1945. (*b*) Lyons, C.: Penicillin Therapy of Surgical Infections in U. S. Army, J. A. M. A. **123**:1007-1018 (Dec. 18) 1943. (*c*) Crisp, L. H.: Allergy to Penicillin, ibid. **126**:429-430 (Oct. 14) 1944.

erythema nodosum type of reaction. Morris and Downing [16] reported severe bullous dermatitis in a patient four days after the last injection of penicillin. We have had 1 case of erythema multiforme with typical lesions on the backs of the hands and the forearms and a few lesions on the front of the thighs and the trunk after injection of penicillin.

Phytid types of reaction after injections of penicillin have been reported by others and have been seen by us. These reactions should be expected in view of Jadassohn's [17] observations that fungi contain specific and nonspecific antigenic fractions, which may sensitize a patient not only to the fungus with which he has been infected but also, parabiotically, to other fungi. Hence, theoretically at least, a patient who has had dermatophytosis of the feet or of the groin may suffer from a "-phytid" type of reaction if he is subsequently given penicillin.

Graves, Carpenter and Unangst [18] have reported 2 patients with histories of dermatitis of the hands, feet or groin and with positive reactions to trichophytin tests, who exhibited typical vesicular "id" reactions on the hands, feet or groin a few hours after each injection of penicillin. Lamb [19] reported 2 similar cases. We have seen this same sequence of events in 3 of our patients and shall discuss it from the industrial angle.

This "-phytid" type of reaction to penicillin has created a problem in the interpretation of industrial liability in certain cases. Dickson [20] referred to us a patient in whom cellulitis of the legs had developed after an industrial injury. Injections of penicillin were given for the cellulitis, whereupon the patient experienced severe vesicular dermatitis of the feet, which had formerly been the site of dermatophytosis but which had been normal at the time of injury. Inasmuch as this dermatophytosis of the feet was secondary to treatment necessary for an industrial injury, it was interpreted by us as industrial in origin and was so accepted by the insurance company. Dickson reported that he had had 3 other similar cases. We have seen, and other physicians have reported to us, mild erythematous reactions in the crural area. These, presumably, may be "ids" at the site of former crural fungous infections.

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16. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, J. A. M. A. **127**:711 (March 24) 1945.

17. Jadassohn, W.; Schaaf, F., and Wohler, G.: Analyses of Composite Antigens by Schultz-Dale Technique: Further Experimental Analysis of Tricophytons, J. Immunol. **32**:203-227 (March) 1937.

18. Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, Arch. Dermat. & Syph. **50**:6-7 (July) 1944.

19. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, Arch. Dermat. & Syph. **52**:93-95 (Aug.) 1945.

20. Dickson, D.: Personal communication to the authors.

Krause [21] has treated 5 patients who experienced industrial contact dermatitis of the hands during the process of manufacture of penicillin. In 1 patient employed in the grinding and bottling department dermatitis of the face, arms and neck developed immediately after the first day of contact with penicillin. This patient had not previously used penicillin. Reactions to patch tests with dry penicillin and with solutions of penicillin were positive. In 4 patients in the processing department dermatitis of the face, hands, wrists or arms developed within three days to three weeks after beginning work with penicillin. All showed strongly positive reactions to patch tests with penicillin solutions.

COMBINED DERMAL AND EPIDERMAL SENSITIZATION

One of us (H. J. T.) [22] discussed combined sensitization of the epidermis and the dermis to the sulfonamide drugs and showed that application of these drugs to the skin could produce contact dermatitis, which, in turn, sensitized the whole organism, so that the patients exhibited dermal reactions in the form of urticaria or toxic erythema when the drug was given by mouth. We observed that this can happen also from the application of penicillin to the skin. We were treating 1 of our colleagues for folliculitis and dermatitis of the beard and prescribed a penicillin solution containing 500 units per cubic centimeter. Within twelve hours there was a violent exacerbation of the dermatitis of the face. This subsided in about a week, at which time a patch test elicited a mildly positive reaction. The dermatitis of the face had disappeared entirely when, two months later, he was given an intramuscular injection of penicillin for a dental infection. This was followed within twelve hours by a severe recurrence of the dermatitis of the face. Within another day a generalized pruritic erythematous urticarial eruption had developed.

A similar case was reported by Kolodny and Denhoff.[23] Their patient suffered an exacerbation of dermatitis of the hand when penicillin ointment was first applied. Twenty-five days later he was given 20,000 units intramuscularly every three hours. After the third injection a generalized erythematous eruption developed. The healing lesions of the preexisting dermatitis of the hand became hyperemic, pruritic, vesicular and wet. Five days later another course of injections of penicillin, of another brand, produced the same types of reactions, and three days later generalized urticaria developed.

In their investigations Kolodny and Denhoff noted that there was a much higher incidence of immediate reactions (25 per cent) to injec-

21. Krause, M.: Personal communication to the authors.

22. Templeton, H. J.: Epidermal and Dermal Sensitization (Co-Existing in the Same Individual), J. A. M. A. **127**:908-911 (April 7) 1945.

23. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058-1061 (April 20) 1946.

tions of penicillin in patients being treated for dermatoses than in nondermatologic patients receiving the injections (6 per cent). This coincides with out experience. We believe that penicillin should not be applied to the skin or injected into patients with certain exudative dermatoses, such as eczema or eczematoid dermatitis, unless there is a clearcut indication for its use, such as superimposed pyogenic infection which has not yielded to older conservative therapy.

MISCELLANEOUS REACTIONS

Miller [24] has reported 4 severe toxic erythema eruptions in patients who were given penicillin orally. He commented on the delayed appearance of the eruption after ten to fourteen days. Maynard [25] told us of a patient who experienced dermatitis around the site of a deltoid muscle into which penicillin in wax and oil had been injected. The arm became edematous from shoulder to wrist.

EXPERIMENTAL STUDIES

Divergent observations have been reported by those who have studied persons reacting to penicillin and normal persons by means of patch, scratch and intradermal tests. As mentioned, Cohen and Pfaff [1] obtained positive reactions to patch tests in 0.95 per cent of normal persons who had never been exposed to penicillin. Most authors have noted positive reactions to patch tests in patients who had contact dermatitis from penicillin. Rostenberg and Welch [26] found tuberculin type of reactions to intradermal injections of penicillin in 5.5 per cent of 144 normal persons who had not had penicillin previously. They were unable to demonstrate circulating antibodies in these persons or in 1 patient with urticaria from penicillin by means of the Prausnitz-Küstner test. The experiments of McGuire [27] suggested a positive transfer of antibodies.

We obtained blood serum from 5 patients who had experienced urticaria after injections of penicillin. The following experiments were performed:

EXPERIMENT 1.—Four female patients received intradermal injections of 0.1 cc. of serum from the 5 urticarial reactors with 0.1 cc. of normal serum as a control. Forty-eight hours later they received intramuscular injections of a single dose of 200,000 units of penicillin in sesame oil. The areas where the serums from persons with urticarial reactions had been injected were observed in twenty-four and in forty-eight hours but reactions were not seen at any of the sites.

24. Miller, H.: Personal communication to the authors.

25. Maynard, M. T.-R.: Personal communication to the authors.

26. Rostenberg, A., Jr., and Welch, H.: A Study of the Types of Hypersensitivity Induced by Penicillin, Am. J. M. Sc. **210**:158-167 (Aug.) 1945.

27. McGuire, J. A.: Localized Sensitivity to Crude Penicillin: Report of a Case, Arch. Dermat. & Syph. **53**:31-33 (Jan.) 1946.

EXPERIMENT 2.—Serums from 5 persons with urticarial reactions were injected intradermally into 7 of our office staff. Forty-eight hours later patch tests of an isotonic solution of sodium chloride containing 1,000 units of sodium penicillin per cubic centimeter were applied to the areas where the serums were injected and were observed daily for a week. Reactions were not seen. This could mean one of two things: first, that there were no circulating antibodies in the serums from those with urticarial reactions, or, second, that there was insufficient transepidermal penetration of the solution of penicillin in the patch test. Because of results in the next experiment we favor the second of these explanations.

EXPERIMENT 3.—The serums from the 5 persons with reactions were injected intradermally into 7 of our office staff. Forty-eight hours later an isotonic solution of sodium chloride containing 1,000 units of sodium penicillin per cubic centimeter was scratched into the areas injected with the serums. Reading at the end of twenty minutes showed 1 plus to 2 plus reactions on the basis of a 1 plus to 4 plus scale as compared with negative reactions in 4 of our staff used as controls. We regarded this as evidence of the presence of circulating antibodies.

CONTROL OF REACTIONS

Cutaneous reactions to penicillin may be lowered in incidence by a knowledge of the danger of penicillin and by a proper selection of cases.

Patients whose skins are in unstable equilibrium because of some exudative dermatoses are poor risks with penicillin either topically applied or injected. If there is present an added secondary pyogenic infection, penicillin may be tried cautiously. If improvement does not occur in three to five days penicillin should probably be discontinued, as longer periods of use are more apt to sensitize the patient. It is permissible to use penicillin topically in simple pyoderma or in impetigo, as it usually effects cures in these diseases in the safe period of the first week, before sensitization is likely to occur.

There is some evidence that a change of brand or of vehicle may prevent further reactions in a patient sensitive to penicillin, but this has not been the experience of most investigators.

The newer antihistamine drugs such as "benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride) or "pyribenzamine hydrochloride" N.N.R. (tripelennamine hydrochloride) may be found to be of value in preventing or in alleviating urticaria from penicillin.

CONCLUSIONS

1. Penicillin given by topical application, by oral ingestion or by injection sensitizes a certain percentage of persons.

2. The reactions most frequently seen are contact dermatitis and urticaria. Other reactions occur.

3. Patch tests, scratch tests, intradermal tests and passive transfer each give varying reactions in patients sensitive to penicillin.

4. Because of its ability to sensitize, penicillin should not be used indiscriminately by dermatologists. In general, its use should be avoided in noninfectious dermatoses. When used with an understanding of its limitations and of its dangers penicillin is valuable in the treatment of certain pyogenic infections of the skin.

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ABSTRACT OF DISCUSSION

DR. CORNELIUS F. LEHMAN, San Antonio, Texas: The first examples of any note of sensitivity to penicillin that I saw were in a general hospital in England in the early part of 1945. These were in about 20 patients who were in the same convoy and who had received, at the time of the secondary closure of wounds, a resumption of penicillin therapy, the primary treatment having been given about three weeks previously as first aid in the forward stations.

My colleagues and I thought then that reactions to such an inert substance were out of the question, and penicillin at first was not blamed. I searched for some other common denominator, such as food. Then I administered a dose of penicillin to a volunteer. In a few hours his urticaria came back with severe angioneurotic edema, which necessitated splitting the cast on his arm, and a painful swelling of the knees and the ankles.

Since then we have been on the lookout for reactions and have discovered that penicillin sensitivity is rather common. The remarkable thing, to me, is that of the thousands of doses of penicillin which were used in the army early in the war so few cases of sensitization were noted. I am sure that that was not because they were overlooked, since when a severe reaction to penicillin develops the patient will tell the physicians about it.

I often have wondered why there are more reactions to penicillin now than were seen earlier in the army, and whether the increase is due to a change in the manufactured product or whether we have a different type of patient with different barometric pressure, heat, humidity and other factors.

I have seen 2 cases of exfoliative dermatitis. "Benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride) has been used with varying results but was not helpful in these 2 cases of exfoliative dermatitis. I have seen a severe reaction with urticaria and angioneurotic edema in a physician, which appeared nine days after the use of penicillin lozenges. In his case a few previous treatments with penicillin spray had probably resulted in sensitization.

To explain the reactions I have frequently tested patients after their recovery with the refined penicillin broth and with trichophytin, and as yet I have not found any explanation that is satisfactory.

I think that the commonest sensitizer will eventually prove to be epidermophytin, particularly in cases of the inflammatory type. Following this hypothesis, I would not be surprised if in the future many cases of violent attacks of asthma after penicillin therapy should occur, particularly in patients with preexisting fungous infections of the lung or the skin.

DR. RICHARD S. WEISS, St. Louis: The most violent reaction to the use of a drug that I have ever seen was in a physician who used penicillin mist for sinusitis. His face was swollen to about twice the normal size; he had fever; he was exceedingly ill. The cause of the disorder was not suspected. It was thought that he had erysipelas, and he was given penicillin intramuscularly. On discovery of the cause he stopped the use of penicillin and recovered in three or four days.

However, I wanted to talk about the results obtained by my colleagues and me at Barnard Free Skin and Cancer Hospital and Washington University, which were published in the March and April 1946 issues of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. Significant statements are contained therein about persons who handle penicillin. Seven workers in a pharmaceutic plant handled the drug, and all 7 gave positive reactions to patch tests when penicillin was applied. They gave negative reactions to patch tests with an acetone extract of the fungus itself. On injecting penicillin into these patients parenterally reaction was not obtained, nor was there any flare-up at the point where previously there had been a positive reaction to a patch test.

We ran a series of patch tests on 200 persons (surgical patients, workers in hospitals and workers in factories). By using the menstruum and the extract of the organism as controls, we found that 4.5 per cent gave positive reactions. We were able to retest some of the subjects who had given a negative reaction ten days to two weeks later. Seventeen of the 60 or 70 subjects whom we retested showed positive reactions. Therefore, we feel that by means of the patch test we were able to produce epidermal sensitivity. Our experiments did not indicate that epidermal sensitivity always is accompanied by vascular sensitivity. Although this possibly can occur, apparently it does not occur often.

I am grateful for having had the opportunity to listen to Dr. Templeton's paper and for the information which he has added to what had already been known and reported.

DR. PAUL E. BECHET, Elizabeth, N. J.: Dr. Templeton and his collaborators are to be congratulated on a timely and valuable contribution. In a recent paper I said that the incidence of sensitization from the local use of penicillin was rare, but I qualified this statement by saying that this rarity might be due to the fact that the drug had been in use only recently and that sufficient time had not elapsed to permit evaluation of attendant accidents. Yet even at this early period Pyle and Rattner, also Binkley and Brockmole, had reported a few cases. I also had observed 2 cases in private practice.

Since January 1946 the incidence of dermatitis after the local use of penicillin has, in my experience, tremendously increased. It is apparently a new medical hazard, as many of the cases observed occurred among physicians and among laboratory workers engaged in the manufacture of penicillin. In the past few months I have seen a dozen or more private patients with severe dermatitis which appeared after local use of the drug. Induced sensitivity from topical use of penicillin occurred in a few patients. In 2 instances the drug had been used for several weeks without any untoward effects; yet weeks after it had been discontinued the same preparation used for relief of a recurrence resulted in severe dermatitis within forty-eight hours.

Penicillin is now being used locally more and more by general practitioners, who have been wrongly assured of complete lack of local reaction by both manufacturers and enthusiasts. In my opinion, the frequency of dermatitis from local use of penicillin will in the near future equal if not exceed the occurrence of dermatitis from the local use of sulfonamide compounds.

DR. UDO J. WILE, Ann Arbor, Mich.: I was glad to hear Dr. Templeton refer to the delayed reactions to penicillin. Short of the few cases of fatal outcome after penicillin therapy, the most serious manifestations I have noted are of edema involving the larynx and the lungs.

The first case that was brought to my attention occurred in a man who had received 2,400,000 units of penicillin. He had remained well and had not had

difficulty during his stay in the hospital. Five days after his discharge he experienced giant urticaria which soon involved the mucous membranes of his mouth. Then laryngeal edema and pulmonary edema developed. Only with difficulty was he assisted to breathe, and for a time it looked as though he might die.

Shortly after his recovery, within two days, he had a relapse, a milder attack of the same thing.

That sort of reaction has been encountered seldom but often enough to indicate that it might be a definite reaction to penicillin. Close to it is the reaction which Dr. Templeton has referred to as a serum-sickness-like reaction, in which, besides general edema and urticaria there is arthritic pain, and occasionally a tendency for hydrops to occur in the joints.

I can recall at least 6 cases of exfoliative dermatitis after administration of penicillin. All, however, were mild and in no way comparable to the exfoliative dermatitis due to arsenic. I dare say that I could tell you of hundreds of cases of exacerbation of Trichophyton infections of the feet in patients who were admitted and treated for syphilis with penicillin. Some of these Trichophyton infections were apparently quiescent and were not noticed on admission. In some instances the eruptions of bullae, erosions and interdigital lesions were so severe that the patients required special treatment for that infection during their stay. So, apparently penicillin does cause exacerbation of ordinary Trichophyton infections of the feet.

Dr. Herbert Rattner, Chicago: I think that Pyle and I were the first to report a case of contact dermatitis from penicillin. It occurred in an army physician who was administering penicillin to patients. At the time we were able with difficulty to obtain some crystalline penicillin for a patch test. In this case we obtained strongly positive reactions from crystalline penicillin and from the whole penicillin product that the physician was using. The liquor medium did not produce a reaction and, therefore, we concluded that in this case the dermatitis was due to sensitivity to the penicillin itself.

We have also observed 4 cases of severe serum sickness type of reaction and a number of cases of urticaria. The reactions seemed to occur in waves. The cases were more numerous just after penicillin was released for civilian use, and since then there seem to have been waves of reactions as though the various stocks of the drug may have played a causative role.

The urticarial type of reaction has generally responded well to treatment with "benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride), but the serum sickness type has not. Until today it was my impression that penicillin could be administered freely and that the danger from its use was overstressed. Pyle and I had not seen any renal block, and there were not any hemopoietic changes, cerebral reactions or other dangerous reactions reported from the use of penicillin. The drug is an eminently useful one, but the report today of 2 fatal reactions from its use changes the picture.

Dr. E. William Abramowitz, New York: I can confirm the observations of Dr. Templeton. To the reactions hitherto reported I would like to add herpes simplex of the face after the use of penicillin for osteomyelitis.

The introduction of new drugs invariably brings in its wake a host of new reactions. In fact, one is almost led to believe that if a drug is going to be of any value, it is bound to produce untoward effects in someone.

Sensitivity to penicillin presents some difficulties not present in cases in which simple chemical drugs are used. We know now that penicillins G, X, F and K are identifiable from one another in the side groups attached to a common nuclear

structure. Commercial penicillin shows differences in the relative proportion of those fractions and in the degree of purity, which seem to have bearing on the antibiotic action of the drug. It may be that sensitivity varies with the individual components of penicillin, the relative proportion of each, or the synergistic effects of the various fractions in combination. Furthermore, the culture medium and the vehicle used in topical application have to be considered also. Another point that I think we need to stress is that penicillin has a photosensitizing action, for eruptions from the drug seem to favor the areas that are exposed to the sun.

In addition to the sensitization that develops in patients receiving penicillin, there is an increasing number of workers, nurses and physicians handling penicillin who experience dermatitis. In Dr. Rosen's service at the Skin and Cancer Unit 3 of my associates and I became sensitized through the handling of penicillin. An annoying dermatitis of the face develops, precluding the handling of penicillin by such sensitized persons with the ordinary open methods. Methods of prevention of sensitization would be welcome. I am now using the Abbott syringe, so that I am not in contact with the drug or its vehicle.

I will go further than Dr. Rattner and say that while the reactions from penicillin are not so serious as from the sulfonamide drugs, I would not use penicillin in minor infections of the skin. I would reserve the use of penicillin for the more serious pyodermas, as I have advocated previously in the case of the sulfonamide drugs. It must be emphasized, in the meantime, that promiscuous use of the drug is unwise and hampers the use of a valuable agent when needed in the serious diseases due to organisms that are susceptible to penicillin.

Dr. Martin F. Engman Jr., St. Louis: A group of us in St. Louis have conducted and published a clinical study of locally applied penicillin. A good deal of the work was done in the private office shared by Dr. Engman Sr. and me. We used penicillin ointment. Ten per cent of our subjects were irritated, usually rather severely. In patch tests, penicillin itself was found to be the offending agent.

There were no remarkable therapeutic results. Penicillin salve did not seem better as a therapeutic agent than older remedies such as microform sulfathiazole. It about equaled mercury or bismuth tribromphenate in impetigo. We do not use either penicillin salve or sulfathiazole in our office at present, since both are such strong sensitizers.

Dr. Herbert S. Alden, Atlanta, Ga.: Our experience with penicillin among combat forces in the United States Navy in the Philippines was similar to Dr. Lehmann's experience. For a period of some six weeks, we gave an average of 12,000,000 to 20,000,000 units of penicillin to men with combat injuries each day, and during that period I do not recall an instance in which we could consider penicillin a sensitizing agent.

After V-J Day we had some penicillin in excess. We began using it in a water-miscible base (the water-soluble base used by the United States Army or the base in any of the common shaving creams for impetigo and pyoderma). We would observe, as Dr. Rattner mentioned, waves of irritation after its use, and on investigation it seemed that the penicillin ointment which was prepared and left out on the counter (which was frequently true on a busy day) for more than forty-eight hours was the ointment that produced the irritation.

I have since felt (and it is just an impression) that the commercial penicillin ointments that had been on the druggist's counter for any length of time frequently produced irritation. Hence, in Atlanta, I have a druggist make up my penicillin ointment in a water-miscible base at regular intervals. I have noticed

that this ointment may irritate when left over the week end. Patients to whom penicillin ointment is given on Monday or Tuesday will sometimes be irritated, whereas patients to whom the ointment is given in the middle of the week, when it was freshly made, do not have irritation.

DR. MARTIN T. VAN STUDDIFORD, New Orleans: In the Marine Hospital penicillin was used for patients with gonorrhea. Some of these patients had had two or three courses of penicillin therapy at different places. One young man experienced a severe reaction from penicillin. After two weeks an intern applied a patch test on the patient's arm; edema of the epiglottis resulted. Only with a great deal of effort was a tracheotomy avoided.

The most peculiar reaction to penicillin that I have seen was in a sailor with a big ship tattooed on his chest. He had an urticarial rash in some of the tattoo marks. He was sensitive about his tattoo and would not let us take a section or a picture. I should like to have known what chemical was embedded in his skin that would have given him that reaction.

DR. FRANK C. COMBES, New York: One reaction accompanying the administration of penicillin has not been mentioned, and I think it is one which we should take into consideration. What reaction will follow the administration of penicillin in beeswax? What is going to happen to the beeswax?

A number of years ago a group of us injected into the arms of some patients epinephrine in beeswax to produce slow absorption. Two or three years afterward lumps developed around the wrists of these patients and on the backs of their hands. The beeswax had not been absorbed. It had gradually worked down the fascial planes, and in some instances it was necessary to remove the beeswax surgically.

Many reactions to penicillin, I think, depend on dosage. It is possible that at present the use of penicillin is more or less experimental. It is possible that in larger doses it would be more effective. I know of a severe reaction to penicillin in a patient with ocular pemphigus, an acute fulminating type of disease. In view of the good results obtained from large doses in bacterial endocarditis, we gave this patient 1,000,000 units a day. After four or five days she experienced severe angioneurotic edema. I do not believe that I have ever seen such collections of fluid in the joints, and the patient suffered excruciating pain. That was after she had received 6,000,000 units in six days.

I agree with Dr. Engman in some respects regarding the topical application of penicillin. We have discontinued penicillin as an ointment in the formulary of Bellevue Hospital, for which there are several reasons. Dr. Engman has already mentioned one. The other is the difficulty of finding a base which is relatively stable. However, I will say that penicillin in powder form in polyethylene glycol dispersion is the finest treatment which I know for impetigo. There is nothing which remotely approaches the rapidity with which impetigo responds to it. In some cases severe lesions will disappear after two or three applications, within twelve hours. The lesions will dry up, and it is unusual for any case to persist more than three or four days. Penicillin powder is irritating, but in polyethylene glycol it is nonirritating and is slowly liberated. Polyethylene glycol is soluble in serum, and the results are excellent.

DR. GEORGE M. LEWIS, New York: Acting on our own clinical observations, which corroborate the observations of Dr. Templeton and Dr. Wile, that dermatophytid and sometimes dermatophytosis-like reactions occur after administration of penicillin, my colleagues and I instituted a short series of experiments with animals which will be reported before the Society of Investigative Dermatology.

The results of these experiments indicate that a superficial fungous infection may sensitize the skin so that the later administration of penicillin may provoke cutaneous reactions.

DR. FREDERICK R. SCHMIDT, Chicago: Just to complete the record, I would like to suggest the possibility of the use of penicillinase in these cases. I do not know how it could be used, but it is an agent which neutralizes penicillin promptly.

DR. H. J. TEMPLETON: I want to thank the various discussers for their generous contribution to my knowledge of this subject. I think I have learned more than I gave you. I have learned about the fatal reactions with which I had not had experience, such as generalized exfoliative dermatitis.

If you are doing any experimental work with patch tests, or if you are attempting passive transfer, you might remember that Kolodny and Denhoff showed that they did not get good patch tests, scratch tests or passive transfer unless they used, I think it was, 2,500 units per cubic centimeter. We were working with only 1,000 units per cubic centimeter.

I am aware of the dangers of penicillin, and I agree with Dr. Abramowitz and Dr. Engman that maybe it should not be used topically. I left a loophole in my paper, thinking that penicillin might be used with great care because of the excellent results which we have had in impetigo. For this disease we prescribe an aqueous solution of penicillin, 500 units per cubic centimeter administered with a DeVilbiss atomizer, and we tell the patient to spray the face three or four times a day. I have never seen anything work as rapidly in impetigo and with as little messiness.

THERAPY OF EARLY SYPHILIS WITH MASSIVE DOSES OF PENICILLIN

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WHEN Ehrlich introduced arsphenamine (N. N. R.) in 1909 it was his sincere hope that syphilis could be cured with a single injection of the drug. It soon became apparent that one injection was woefully inadequate and, moreover, that three, six or even more injections failed to yield the desired result. With the introduction of bismuth as a powerful ally, the campaign against syphilis moved closer to its goal.

Two decades after Ehrlich's discovery, following the admirable work of the Clinical Cooperative Group,[1] it was generally recognized that the use of alternating courses of the arsenicals and bismuth preparations, given continuously over a period of approximately twelve to eighteen months, in a large percentage of cases, gave the result which Ehrlich had sought in vain.

From the office of the President of the Chicago Board of Health and the Chicago Intensive Treatment Center, Venereal Disease Control Program, in cooperation with the United States Public Health Service.

1. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Taliaferro, C.; Parran, T., and Usilton, L. J.: Cooperative Clinical Studies in the Treatment of Syphilis, Ven. Dis. Inform. **13**:207 (June 20); 253 (July 20); 317 (Aug 20); 351 (Sept. 20); 371 (Oct. 20); 389 (Nov. 20) 1932.

In the early 1930's, a group of physicians [2] once again envisioned the possibility of eradicating syphilis in a short time by utilizing an intensified treatment—the "five day drip." A short time later, another group of investigators [3] sought to compress the treatment of early syphilis into one day, taking advantage of the therapeutic synergism of combining the arsenicals with physically induced fever.

At the onset of World War II, it was clearly recognized that long term routine antisyphilitic treatment could not cope with the threatened rise in venereal disease rates. From the standpoint of public health, it was deemed imperative to apply more widely the various intensive forms of treatment. Accordingly, centers were established throughout the country by the United States Public Health Service for the treatment of infectious syphilis in a relatively short time, arsenical and bismuth preparations with or without fever therapy being used.

In 1943, a clarion call was sounded by Mahoney, Arnold and Harris,[4] heralding an entirely new way of treating syphilis. Overnight the imagination of the medical world was fired by the dazzling prospect of a new and potent weapon in the battle against syphilis which dwarfed all previous drugs by virtue of its nontoxicity.

Numerous schemes of treatment came immediately to mind, and, indeed, many of them were projected into actuality. It was inevitable that Ehrlich's dream should flash forth again, embodying a new champion—penicillin.

Recent studies reported by Arnold [5] indicated that syphilitic rabbits treated with relatively massive doses of penicillin over periods of from twelve to twenty-four hours could be rendered nonsyphilitic. Thus, of 18 animals given 15,000 units at hourly intervals for twenty-four hours, 15 were successfully treated and in only 3 could any evidence of syphilis be found. The great differences in the course of the disease in rabbits as contrasted with that in human beings being recognized, an investigation was launched to determine the effect on human syphilis of massive doses of penicillin given over a short period.[6]

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2. Hyman, H. T.; Chargin, L., and Leifer, W.: Massive Dose Arsenotherapy of Syphilis by Intravenous Drip Method: Five Year Observations, Am. J. M. Sc. **197**:480 (April) 1939.

3. Simpson, W. M.; Kendell, H. W., and Rose, D. L.: The Treatment of Syphilis with Artificial Fever Combined with Chemotherapy, Ven Dis. Inform., 1942, supp. 16, p. 1.

4. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**:355 (Dec.) 1943.

5. Arnold, R. C.: Personal communication to the authors.

6. Schwemlein, G. X.; Barton, R. L.; Bauer, T. J.; Loewe, L.; Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. **130**:340 (Feb. 9) 1946.

A group of 129 patients exhibiting clinical evidence of primary or secondary syphilis was treated with 10,000,000 units of penicillin, administered by intravenous drip over a twenty-four hour period, from March 28 to Aug. 2, 1945. All revealed lesions which on dark field examination were positive for Treponema pallidum.

The ages of the patients ranged from 15 to 48 years: 62 per cent were 25 or under; 80.7 were 30 or under. Of these patients 119 were previously untreated for syphilis. The remaining 10 had received varying amounts of arsenical and bismuth preparations and subsequently exhibited clinical and laboratory evidence of relapse or had failed to show negative results on dark field examination.

Eligibility for treatment was determined on the basis of freedom from detectable pathologic changes of the cardiovascular, pulmonary, urinary and hemopoietic systems. Electrocardiograms and roentgenograms taken at a distance of 2 meters were included in the pretreatment medical survey. Examinations of cerebrospinal fluid were performed routinely before treatment.

The administration of penicillin by the intravenous drip technic is known to cause thrombophlebitis [7]; therefore an attempt was made to circumvent this complication by the use of the anticoagulant heparin, incorporated in the "Pitkin menstruum." [8] Three hundred milligrams of heparin was injected subcutaneously into the anterolateral aspect of the thigh immediately before the patients were given the intravenous drip by the usual technic, the veins of the forearms being utilized. The rate of flow of the solution was regulated by means of a pinch clamp to deliver 1,000 cc. of solution continuously over a twenty-four hour period. The levels of penicillin in the blood and cerebrospinal fluid as previously reported [6] were determined by the method described by Rosenblatt, Alture-Werber, Kashdan and Loewe.[9]

Further treatment was not given unless clinical or serologic relapse or pregnancy occurred. The last patient treated received therapy on Aug. 2, 1945. Therefore the maximal period of observation ranges from seven to eleven months.

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7 Anderson, G. D.: The Treatment of Infections with Penicillin, New England J. Med. **232**:400 (April 5) 1945. Keefer, C. S.; Blake, F. G.; Marshall, E. J., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: Report of Five Hundred Cases, J. A. M. A. **122**:1217 (Aug. 28) 1943.

8. Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin: Preliminary Report, Am. J. M. Sc. **208**:54 (July) 1944.

9. Rosenblatt, P.; Alture-Werber, E.; Kashdan, F., and Loewe, L.: A Method for the Determination of Penicillin Levels in Body Fluids, J. Bact. **48**:599 (Nov.) 1944.

Of the patients 105 were Negro, of whom 68 were men and 37 women; 24 were white, of whom 17 were men and 7 women. Of the total number of cases, the conditions in 15 were in the seronegative primary stage and in 29 in the seropositive primary stage. Of the 85 patients in this series with secondary syphilis, 80 had early secondary syphilis and 5 exhibited late relapsing secondary syphilis.

Inasmuch as it is of interest to ascertain the promptness of relapse following treatment with a given scheme, the table reveals the relapse in the entire group at monthly intervals.

Number and per Cent of Patients with Early Syphilis Treated with 10,000,000 Units of Penicillin from March 28 Through Aug. 2, 1945, Showing Number of Months After Treatment in Which Relapse Occurred

Observation Period, Mo.	Total		Failures					Clinically Negative				Status Unknown	
			Total		Serologic	Probable Clinical	Probable Reinfection	Seropositive		Seronegative			
	No.	%	No.	%				No.	%	No.	%	No.	%
1	129	100.0	2	1.5	..	2	..	87	67.4	10	7.8	30	23.3
2	129	100.0	17	13.2	1	15	1	66	51.2	12	9.3	34	26.3
3	129	100.0	38	29.5	8	29	1	38	29.5	13	10.0	40	31.0
4	129	100.0	51	39.5	11	39	1	23	17.8	16	12.4	39	30.3
5	129	100.0	55	42.6	14	40	1	19	14.7	17	13.2	38	29.5
6	129	100.0	59	45.7	15	43	1	11	8.5	21	16.3	38	29.9
7	129	100.0	61	47.3	15	45	1	8	6.2	24	18.6	36	27.9

In 36 of the 129 patients included in "status unknown" observation was terminated for the following reasons: Two were inducted into the armed forces, 9 moved out of jurisdiction, 2 became pregnant, 4 were committed to jail and 19 we were unable to locate. Tests of the serum of these 36 patients gave negative results at the time of the last examination before they were lost to observation.

Not infrequently a patient failed to report to the hospital during one month and returned the following month. This accounts for the fluctuation in the column "status unknown" in the table.

COMMENT

It is apparent from the table that the rate of failure with this form of treatment under the conditions given in this experiment is so high as to render such treatment unsuitable for early syphilis. For 61 of the 129 patients discussed the treatment was a failure. Thirty-six of the 129 patients were not accounted for, having lapsed from observation. It is reasonable to assume that for some of these also the treatment was a failure.

It is interesting to note the relatively short time required for relapse to develop. Thus, in 51 of the 129 patients treated relapse occurred in four months or less.

It is worthy of comment that schemes of treatment employing as little penicillin as 600,000 units in seven and one-half days [10] or 1,200,000 units in three and three-quarters days [11] yielded significantly superior results than the large dose of 10,000,000 units over a twenty-four hour period given intravenously in this series.

As might have been anticipated, results were better for patients with seronegative primary syphilis than for those with either seropositive primary or secondary syphilis. Thus, of 15 patients presenting seronegative primary syphilis, only 5 (33.3 per cent) relapsed at the end of seven months. Of 29 patients with seropositive primary syphilis who were treated, 13 (44.8 per cent) relapsed at the end of seven months, and of 85 patients with secondary syphilis 43 (50.6 per cent) relapsed.

SUMMARY

1. One hundred and twenty-nine patients who were found on dark field examination to have primary or secondary syphilis were treated with 10,000,000 units of sodium penicillin intravenously over a twenty-four hour period.

2. Ten million units of penicillin given intravenously in a twenty-four hour period in this series proved to be grossly inadequate in the therapy of early syphilis.

Mr. John L. Smith, of Charles Pfizer and Co., Inc., showed keen interest and gave valuable suggestions and constant cooperation. Through him we obtained the generous supply of penicillin utilized in these experimental studies. Dr. H. C. McCraney and Dr. Lydia Marshak gave assistance, and the technical work of Elsie Miller, B.A.; Ellen Bienfang, R.N., and Mary Gleason made this study possible.

54 West Hubbard Street.

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10. Bauer, T. J.; Bundesen, H. N.; Craig, R. M.; Schwemlein, G. X., and Barton, R. L.: The Treatment of Early Syphilis with 600,000 Units of Penicillin in Seven and One-Half Days, Am. J. Syph., Gonor. & Ven. Dis. **31**:45 (Jan.) 1947.

11. Craig, R. M.; Schwemlein, G. X.; Barton, R. L.; Bauer, T. J., and Bundesen, H. N.: Penicillin in the Treatment of Early Syphilis: Four Hundred and Twenty-Nine Patients Treated with 1,200,000 Units in Ninety Hours, to be published

PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

III. The Therapeutic Activity of Penicillin by Oral Administration

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With the Technical Assistance of Anna M. Rule and Albert J. Paul

PHILADELPHIA

PENICILLIN by oral administration has not been reported on in the treatment of experimental or human syphilis. However, in view of the results observed in treatment of gonorrhea, pneumonia and other bacterial diseases of human beings by this route of administration, it was thought advisable to ascertain the possible therapeutic activity of penicillin in the treatment of experimental syphilis of rabbits by oral administration.

METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of Treponema pallidum. Acute orchitis developed in all, with strongly positive results on dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of forty-nine days. At the expiration of this period the popliteal lymph nodes of surviving animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

The penicillin employed was a commercial amorphous sodium salt with an assay potency of 544 units per milligram, containing 88 per cent penicillin G, supplied by the Commercial Solvents Corporation (lot no. 45072102). For administration, solutions were freshly prepared in isotonic solution of sodium chloride containing 2,000 units per cubic centimeter.

Anhydrous sodium citrate was chosen as an antacid. Solutions were prepared in distilled water containing 0.1 Gm. per cubic centimeter. For administration the dose of penicillin per kilogram of weight was mixed with 2 cc. of the citrate solution (0.2 Gm.) and given by stomach tube at 9 a. m., 1 p. m., and 3 p. m. on each of ten days in succession, totaling thirty doses for each animal. As previously reported by Kolmer, Brown and Rule,[1] the free hydrochloride acid of the stomach

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From the Research Institute of Cutaneous Medicine.

1. Kolmer, J. A.; Brown, H., and Rule, A. M.: The Oral Administration of Potassium Bismuth Tartrate in the Treatment of Experimental Syphilis of Rabbits with a Note on the Gastric Chemistry of Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **21**:387 (May) 1937.

of normal rabbits varies from 0 to 60 units, while the total acidity varies from 122 to 213 units, the units being in terms of cubic centimeters of decinormal sodium hydroxide required for the neutralization of the free hydrochloric and total acids per hundred grams of stomach contents. Under the conditions it was thought that the simultaneous administration of 0.2 Gm. of anhydrous sodium citrate with each dose of penicillin was sufficient.

Serum assays employing hemolytic Staphylococcus aureus (H) were conducted with blood removed one hour after the second and eighth doses.

RESULTS OBSERVED

As shown in the table, 3 rabbits were employed for each dose of penicillin, the doses per kilogram of weight being 500, 1,000, 5,000, 10,000, 15,000 and 20,000 units. It will be observed that all 3 rabbits given 500 units per kilogram per dose for thirty doses, totaling 15,000 units, showed temporarily negative results on dark field examinations but that all relapsed and gave positive results on transfer of lymph nodes. One hour after the second dose the serum assays showed approximately 0.5 unit per cubic centimeter, and they showed 0.5 to 1.0 unit per cubic centimeter an hour after the eighth dose.

All 3 rabbits given 1,000 units per kilogram per dose for twenty-one to thirty doses, totaling 21,000 to 30,000 units, gave negative results on dark field examination, but 2 of the rabbits surviving forty-nine days showed positive results on transfer of lymph nodes. One hour after the second dose serum assays showed 0.25 to 0.51 unit per cubic centimeter, and they showed about 1.0 unit per cubic centimeter one hour after the eighth dose.

All 3 rabbits given 5,000 units per kilogram per dose for thirty doses, totaling 150,000 units, gave negative results on dark field examination, but all showed positive results on transfer of lymph nodes. Serum assays of blood removed one hour after the second dose showed about 0.51 unit per cubic centimeter, and they showed from 0.25 to 0.5 unit one hour after the eighth dose.

Three rabbits given 10,000 units per kilogram per dose for thirty doses, totaling 300,000 units, gave negative results on dark field examination, but all showed positive results on transfer of lymph nodes. Serum assays conducted with blood removed one hour after the second dose showed 0.51 to 2.0 units per cubic centimeter, and they showed 0.5 to 1.0 unit per cubic centimeter one hour after the eighth dose.

Three rabbits given 15,000 units per kilogram per dose for thirty doses, totaling 450,000 units, showed negative results on dark field examination and 1 of these showed a negative results on transfer of lymph nodes. Two rabbits given 20,000 units per kilogram per dose,

Penicillin by Oral Administration in the Treatment of Acute Syphilitic Orchitis of Rabbits

No.	Dose, Units per Kg.	No. of Doses	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days *										Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	42	49	
1	500	30	15,000	2	1	—	—	4	4	4	4	4	4	Positive
2	500	30	15,000	2	2	—	—	3	4	4	4	4	4	Positive
3	500	30	15,000	3	1	—	—	4	4	4	4	4	4	Positive
4	1,000	30	30,000	1	—	—	—	—	—	—	—	—	—	Positive
5	1,000	21	21,000	2	1	—	Died	..	..	..	..	..	..	Not done
6	1,000	30	30,000	2	—	—	—	—	—	—	—	—	—	Positive
7	5,000	30	150,000	1	—	—	—	—	—	—	—	—	—	Positive
8	5,000	30	150,000	2	—	—	—	—	—	—	—	—	—	Positive
9	5,000	30	150,000	2	—	—	—	—	—	—	—	—	—	Positive
10	10,000	30	300,000	1	—	—	—	—	—	—	—	—	—	Positive
11	10,000	30	300,000	1	—	—	—	—	—	—	—	—	—	Positive
12	10,000	30	300,000	1	—	—	—	—	—	—	—	—	—	Positive
13	15,000	30	450,000	1	—	—	—	—	—	—	—	—	—	Negative
14	15,000	30	450,000	1	—	—	—	—	—	—	—	—	—	Positive
15	15,000	30	450,000	1	—	—	—	—	—	—	—	—	—	Negative
16	20,000	30	600,000	1	—	—	—	—	—	—	—	—	—	Negative
17	20,000	30	600,000	1	—	—	—	—	—	—	—	—	—	Negative
18	20,000	42	480,000	1	—	—	—	Died	..	..	..	..	..	Not done

* After treatment was instituted: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examination.

totaling 600,000 units, also yielded negative results on dark field examination and showed negative results on transfer of lymph nodes. In spite of these large doses, however, serum assays conducted one hour after the second and eighth doses showed no more than approximately 0.5 unit of penicillin per cubic centimeter.

COMMENT

In the circumstances, even relatively small doses of penicillin by oral administration, such as 500 units per kilogram, three times a day for a total of thirty doses (15,000 units) may yield temporarily negative results on dark field examinations. However, the minimal curative dose in the treatment of acute syphilitic orchitis of rabbits, on the basis of the results of transfer of lymph nodes, was between 15,000 and 20,000 units per kilogram three times a day for thirty doses, totaling between 450,000 and 600,000 units.

As previously reported,[2] the minimal curative dose of the compound in isotonic solution of sodium chloride by intramuscular injection was approximately 1,000 units per kilogram twice daily for eight days in succession, totaling 16,000 units. It is highly probable that the simultaneous administration of oxophenarsine hydrochloride or bismuth and potassium tartrate U.S.P. would have materially reduced the minimal curative dose of penicillin by oral administration through additive or synergistic effects. However, so far as penicillin alone by oral administration is concerned, a total minimal curative dose of approximately 500,000 units per kilogram in the treatment of acute syphilitic orchitis of rabbits would correspond to between 30,000,000 and 40,000,000 units in the treatment of early syphilis of human adults if the total dose required for the biologic cure of the latter was the same as that for acute syphilis of rabbits; this, however, is far from being true, since these animals require less per kilogram of weight. In the circumstances there appear to be no indications for oral penicillin therapy in the treatment of human syphilis unless, perhaps, it is subsequently learned that oral administration in conjunction with the administration of oxophenarsine hydrochloride or bismuth and potassium tartrate for additive or synergistic therapy is useful and acceptable under certain conditions.

SUMMARY

1. Relatively small doses of penicillin by oral administration, such as 500 units per kilogram three times daily for ten days in succession,

2. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil–Beeswax by Intramuscular Injection, Arch. Dermat. & Syph. **55**:741 (June) 1947.

totaling 15,000 units per kilogram, yield temporarily negative results on dark field examinations in the treatment of acute syphilitic orchitis of rabbits.

2. The minimal curative dose, however, according to the method of administration employed, varied between 15,000 and 20,000 units per kilogram three times daily for ten days in succession, totaling 450,000 to 600,000 units per kilogram.

3. Under the circumstances the oral administration of penicillin in the treatment of human syphilis appears to be contraindicated unless, possibly, it is combined with oxophenarsine hydrochloride or bismuth therapy for additive or synergistic effects in selected cases of the disease.

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PRENATAL SYPHILIS

Its Prevention by Use of Penicillin in Treatment of Pregnant Women with Early Infectious Syphilis

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TWO REPORTS have been published recently,[1] showing spectacularly favorable results in the prevention of prenatal syphilis with the use of penicillin in the treatment of syphilitic pregnant women. It is well known that mothers with syphilis which is beyond the infectious state may deliver normal nonsyphilitic children in a varying but large percentage of cases. Transmission of syphilis to the fetus occurs much more frequently when pregnant women have syphilis in the early infectious stages than in the later stages of the disease. The efficacy of any therapeutic procedure in preventing prenatal syphilis, therefore, will be evaluated most reliably by the effect on the offspring of mothers who during pregnancy had indisputable early infectious syphilis.

When rigidly selected, the number of patients whom we saw who had proved infectious syphilis during pregnancy was limited. To obtain a satisfactory number of cases for evaluation it is necessary to compile the studies which have been made at various institutions.

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1. (*a*) Ingraham, N. R.; Stokes, J. H.; Beerman, H.; Lentz, J. W., and Wammock, V. S.: Penicillin in the Syphilitic Pregnant Woman, J.A.M.A. **130**:683 (March 16) 1946. (*b*) Goodwin, M. S., and Moore, J. E.: Penicillin in the Prevention of Prenatal Syphilis, ibid. **130**:688 (March 16) 1946.

Goodwin and Moore [1b] have already made such a compilation of the results of their own "Baltimore group" comprising 31 women with infectious syphilis during pregnancy (33 infants) and 26 women who were critically selected for infectious syphilis during pregnancy (27 infants) from the "Philadelphia group."

Since the total number in the two groups to date amounts to only 57 mothers with 60 infants, it appears of value to report the observations which were made at the Chicago Intensive Treatment Center on a comparable group ("Chicago group") of 36 women who were treated with penicillin for infectious syphilis during pregnancy and the effect of treatment with penicillin on their offspring.

The patients who were used in this project were selected with the following limitations. All mothers presented lesions of early infectious syphilis, and the presence of syphilis was confirmed by dark field examination in all cases, except 1, in which there were lesions indubitably characteristic of secondary syphilis but unsuitable for dark field examination. The infants were born not more than seven and one-half months after the diagnosis of syphilis and the beginning of treatment of the mother with penicillin. Antisyphilitic agents, other than penicillin were not administered to the mothers during the pregnancies, nor was the intensive course of treatment with penicillin repeated unless there was serologic or clinical evidence of relapse.

Out of a total of 265 syphilitic pregnant women, 42 fulfilled the aforementioned conditions and were due to have delivered by the date of this report (June 1, 1946). Of the 42 infants, 36 either were examined by us, or satisfactory reports of the status of these infants were secured. The other 6 infants either were moved from Chicago or could not be located. The present report is limited to the 36 infants and their mothers.

Inasmuch as it is pertinent to this study to compare the results of treatment of syphilitic pregnant women by one or another of the intensive forms of arsenotherapy with the results obtained by the use of penicillin alone, our tables were arranged after the pattern set by Goodwin and Moore.[1b] Thus, the results of treatment of the Chicago group are easily comparable with results for the Baltimore and Philadelphia groups (table 1).

Two summary tables (2 and 3) were prepared to compare the results of treatment with penicillin and with intensive arsenical therapy during pregnancy in preventing prenatal syphilis. In table 2 the results for the three groups that were treated with penicillin (Philadelphia, Baltimore and Chicago) were combined and compared with the results for the groups that received intensive arsenical therapy as compiled by Goodwin and Moore [1b] from the literature. In table 3 are presented the results of our examinations of 28 infants who were delivered of a

group of 28 women with infectious syphilis during pregnancy who (before the advent of penicillin) had received intensive arsenotherapy (form of treatment described by Eagle and Hogan, that of Schoch or fever chemotherapy).[2] These patients came from the same socio-economic level, had the same racial origin and were selected for early infectious syphilis by the same criteria as were the patients in the penicillin group.

The results of this Chicago arsenical group, therefore, are strictly comparable to the results of the Chicago penicillin group. Tabulated side by side, they give the second opportunity for comparing the results

TABLE 1.—*Number of Infants Examined and Results of Treatment*

Group	Type of Treatment	Number of Infants Born	Infants Born Alive, Apparently Normal	Infants with Syphilis	Infants Born Alive, Normal at Follow-Up		
					Physical	Roentgenologic	Serologic
Philadelphia	Penicillin.....	27*	26	1	26	26	26
Baltimore	Penicillin.....	33†	33	0	33	All examined	33
Chicago	Penicillin.....	36‡	34	0 (1 stillborn)	34	All examined	33
Total.....		96	93	1 and 1 stillborn; probably syphilitic	93		92
Chicago							
Modified form described by Eagle and Hogan		18	18§	2	18‖	15‖	18‖
Fever; 6 hr., temp. 106 F. (r.), 60 mg. oxophenarsine hydrochloride, 150 mg. bismuth compound.....		6	6	1	6¶	5¶	6¶
1,080 to 1,200 mg. oxophenarsine over 8 to 14 days (Schoch).....		4	4#	0	4	3	4
Total (intensive arsenotherapy)...		28	28	3	28	23	28

* One died at 7 months of age of acute febrile illness; no evidence of syphilis on autopsy. One mother had two pregnancies, the second infant not included because mother was not infectious.

† One died at 19 weeks of acute nutritional disturbance and sickle cell anemia but was seronegative in reaction.

‡ One died of prolapse of cord and asphyxia; no autopsy; 1 was stillborn.

§ One mother had another child thirteen months after Eagle treatment. At age of 5 months infant's Kahn reaction was negative, and the child was normal on physical examination (not inserted in table).

‖ Two infants with congenital syphilis were included.

¶ One infant with congenital syphilis was included.

One mother delivered another child two years after Schoch therapy. At age of 8 weeks infant's Kahn reaction was negative and physical and roentgenologic examinations showed no abnormalities (not inserted in table).

of treatment with penicillin and intensive arsenical therapy during pregnancy in preventing prenatal syphilis.

In the Chicago group, of the 36 infants who were delivered of mothers whose syphilis was treated with penicillin exclusively, 1 died of

2. Bundesen, H. N.; Bauer, T. J., and Kendell, H. W.: The Intensive Treatment of Gonorrhea and Syphilis, J.A.M.A. **123**:816 (Nov. 27) 1943.

prolapse of the cord and asphyxia. This accident can hardly be attributed to the therapeutic procedure or to syphilitic infection. A second infant was reported stillborn (further information pending). The mother of this stillborn infant had secondary syphilis, as shown by dark field examination, seven weeks before delivery. She was treated with 2,400,000 units of penicillin over a period of fifteen days, starting seven weeks and ending five weeks before delivery. In this mother relapse of her lesions was demonstrated on dark field examination one month after delivery, requiring retreatment with 4,800,000 units of penicillin. Treatment in this case is regarded as a failure.

No signs or symptoms which could be attributed to congenital syphilis were detected in the 34 living infants by thorough physical examinations, serologic tests or roentgenologic studies of the long bones.

TABLE 2.—*Incidence of Prenatal Syphilis After Treatment of Early Infectious Syphilitic Mothers During Pregnancy*

Treatment	Incidence, Percentage	Total Cases
Intensive arsenotherapy	15	150 cases reported in the literature [1b]
Penicillin therapy.....	2.1	95 cases; Baltimore, Philadelphia and Chicago groups combined

TABLE 3.—*Infants Born of Mothers Who Were Treated for Infectious Syphilis During Pregnancy, Chicago Groups*

Treatments	Number of Infants Examined	Infants with Congenital Syphilis	Stillborn	Therapeutic Failures, Percentage
Intensive arsenotherapy	28	3	0	10.7
Penicillin therapy (2,400,000 units or more)	35	0	1*	2.8

* Probably syphilitic.

Three of the 34 infants were reported as possibly premature. One infant was intentionally delivered six weeks prematurely by cesarian section (for bleeding placenta). The placenta was reported normal in appearance. The second infant was born one month prematurely and showed some signs of prematurity at 6 weeks of age. Further examinations at 2½ months and 3½ months of age revealed a perfectly normal infant with negative reactions to serologic tests for syphilis and normal long bones as determined by roentgenologic studies. The third infant was probably born one month too early. No signs of prematurity were detected on later examination.

In a fifteen year study of prematurity at the Lying-In Hospital in Philadelphia, Tyson [3] recently established that the average incidence of

3. Tyson, R. M.: A Fifteen Year Study of Prematurity, J. Pediat. **28**:648 (June) 1946.

premature infants was 9.4 per cent with the highest incidence of 10.2 per cent in 1930 and the lowest of 7.5 per cent in 1933. The incidence of prematurity in our series of mothers who were treated with penicillin was 8.8 per cent. No case of abortion or miscarriage was reported in our series of women who were treated with penicillin during pregnancy. This problem requires evaluation at a future date on the basis of study of a greater number of patients, but we wish to emphasize that our observations thus far do not confirm the belief that treatment with penicillin during pregnancy predisposes women to abortion, miscarriage or premature delivery.

The results for the Chicago group are in perfect agreement with the results for the Philadelphia and Baltimore groups. When the results for the three groups are summarized, there is a total of 96 infants in 1 of whom congenital syphilis developed and 1 of whom was stillborn. This is an over-all incidence of failure to prevent prenatal syphilis of 2.1 per cent. From the reports in the literature, Goodwin and Moore [1b] calculated an incidence of congenital syphilis of 15 per cent after intensive arsenotherapy. The accompanying tables indicate the correctness of Goodwin and Moore's statement, "Penicillin is incomparably superior to metal chemotherapy, no matter how administered, in the prevention of prenatal syphilis."

The contrast between the effects of intensive arsenotherapy and treatment with penicillin in preventing prenatal syphilis is also shown by the results that were obtained with the two Chicago groups of patients. While the number of patients in each group is smaller, the patients who were treated with penicillin and the patients who had intensive arsenotherapy are strictly comparable as to diagnosis and racial and socioeconomic origin.

In the preceding tables, the 59 infants who were considered to be free of infection were followed up for at least two months, and the majority were followed up for longer periods up to a year.

At the time antisyphilitic therapy was started the majority of patients in both groups were pregnant from sixteen to thirty-two weeks. The details are shown in table 4.

The favorable results of treatment with penicillin during pregnancy in preventing prenatal syphilis are surprising in view of the fact that the incidence of relapses in the penicillin-treated mothers is by no means negligible.[4] In the Philadelphia and Baltimore groups it was observed that normal infants, free of any signs of congenital syphilis, were born of mothers who relapsed after treatment with penicillin. One mother of the Philadelphia group had a clinical relapse (spirochetes were observed

4. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, J.A.M.A. **131**:265 (May 25) 1946.

on dark field examination) four weeks after delivery, but the infant remained free of any evidences of syphilis. In the Baltimore group there were 3 women who, in the last trimester of pregnancy, had a serologic but no clinical relapse and were retreated with penicillin. The infants were normal at birth and remained free of congenital syphilis.

Two observations which were made in the Chicago group appear noteworthy. In both cases the mothers had mucocutaneous relapses (spirochetes were revealed on dark field examination) after treatment with penicillin and yet the infants remained free of syphilis.

TABLE 4.—*Duration of Pregnancy at Time Treatment Was Started*

Type of Therapy	Total Number of Patients	Number of Patients Pregnant		
		Less Than 16 Weeks	16-32 Weeks	More Than 32 Weeks
Penicillin	36	3	25	8*
Intensive arsenotherapy	28	5	21	2
Eagle	18	2	14†	2
Schoch	4	1	3	0
Fever, 8 hr. with 150 mg. bismuth compound and 60 mg. oxophenarsine hydrochloride	6	2‡	4	0

* One infant was stillborn; the mother had been treated with 2,400,000 units of penicillin from the seventh to the fifth week before delivery.

† Two infants were congenitally syphilitic. One mother was treated with 1,050 mg. oxophenarsine hydrochloride and 1,050 mg. bismuth compound the thirteenth to the fifth week before delivery. Mother's Kahn reaction was positive before and after delivery; she was retreated eight and one-half months after delivery. The other mother was treated with 1,380 mg. oxophenarsine hydrochloride and 675 mg. bismuth compound the tenth to the second week before delivery. Mother's Kahn reaction was negative three weeks before and two, three, three and one-half, four and five months after delivery. Serologic relapse and retreatment occurred one and one-half years after delivery.

‡ One infant was congenitally syphilitic. The mother was treated with fever-chemotherapy five months before delivery. The mother showed a negative (Kahn) reaction six, four and three weeks before delivery. There was mucocutaneous relapse seven weeks after delivery, and retreatment.

REPORT OF CASES

CASE 1.—A 14 year old pregnant Negro girl with secondary syphilis (spirochetes were present on dark field examination) was treated with 2,400,000 units of penicillin over fifteen days, twenty-one to nineteen weeks before delivery (May 17 to June 1, 1945). Her Kahn titer of 280 units on admission declined but remained at 40 units. On August 13 she presented herself, having relapsing secondary syphilis. The Kahn titer had risen to 200 units. In view of the advanced pregnancy 9,000,000 units of penicillin over a period of fifteen days was given in retreatment, six to four weeks before delivery (August 13 to August 28). On September 26, the patient delivered a full term, apparently normal, male infant, weighing 5 pounds ½ ounce (2,282 Gm.). The placenta was reported normal. The infant's serologic reactions were negative at the ages of 1 week, 3½ months and 8 months. A roentgenogram of the long bones revealed no evidence of syphilis. Physical examination revealed a lichen urticatus but no signs or symptoms of congenital syphilis. It is remarkable that the infant's reactions remained seronegative despite the mother's relapse, which is shown in the following tabulation:

1 day before delivery	20 Kahn units
1 week after delivery	Positive Kahn and negative Wassermann reactions
8 weeks after delivery	120 Kahn units

CASE 2.—A 19 year old pregnant Negro girl with secondary syphilis (dark field examination revealed spirochetes) was treated with 2,400,000 units of penicillin over a period of fifteen days, sixteen to fourteen weeks before delivery (Oct. 19 to Nov. 3, 1945). On Jan. 10, 1946, she delivered a full term, apparently normal, male infant, weighing 5 pounds 13¾ ounces (2,658 Gm.). The infant's serologic reactions were negative at the ages of 6 weeks and 4½ months. A roentgenogram of the long bones did not show evidence of syphilis. At the age of 6 weeks the infant had a faint atypical eruption on the trunk and the extremities, leaving some slightly hyperpigmented spots at the age of 8 weeks. Otherwise, the physical examination of the infant did not reveal any abnormalities at the ages of 6 weeks, 8 weeks and 4½ months.

The mother, who had had quantitative Kahn reactions of 40 and 20 units, respectively, on admission, was reported as having a positive Kahn reaction one week after delivery. Five weeks after delivery this mother had relapsing secondary syphilis, confirmed by dark field examination. The Kahn titer had risen to 80 units. She was retreated with 4,000,000 units of penicillin over a period of eight days. A comparison of the Kahn reactions of the mother and the infant after delivery is noteworthy.

After Delivery	Mother	Infant
5 weeks	80 (relapse)	—
6 weeks	—	0
7½ weeks	80	—
4th to 5th month	20	0

These observations and similar ones which were made in the Philadelphia and Baltimore groups indicate that treatment with penicillin during pregnancy may prevent prenatal syphilis, even though the mother is not cured and subsequently relapses with lesions showing spirochetes on dark field examination. It has been shown recently [5] that penicillin which is given to pregnant women passes to the fetus in relatively large quantities as early as the tenth week of gestation.[6] Apparently, the amount of penicillin which is transmitted from the mother to the fetus may be sufficiently great to protect or possibly cure the fetus, even though the amount of penicillin that is circulating in the mother's blood fails to eradicate the maternal infection.

This is a progress report giving the most important observations which have been made thus far. Many details will be discussed at a later date when a greater number of patients will have been treated and the infants observed for a longer period of time.

SUMMARY

In a group of 35 infants that were delivered of women who were treated with penicillin for early infectious syphilis during pregnancy, congenital syphilis did not develop in any infant. One infant was still-

5. Hutter, A. M., and Parks, J.: The Transmission of Penicillin Through the Placenta: A Preliminary Report, Am. J. Obst. & Gynec. **49**:663 (May) 1945.

6. Woltz, J. H. E., and Wiley, M. M.: The Transmission of Penicillin to the Previable Fetus, J.A.M.A. **131**:969 (July 20) 1946.

born, possibly because of syphilitic infection (2.8 per cent failures). In a strictly comparable group of 28 infants that were delivered of women with early infectious syphilis during pregnancy who were treated by various methods of intensive arsenotherapy, definite congenital syphilis (10.7 per cent failures) developed in 3 infants.

These observations on the Chicago group are in perfect agreement with the observations on the Philadelphia and Baltimore groups. The results for the three groups combined give an over-all incidence of 2.1 per cent of failure to prevent prenatal syphilis by the use of penicillin in the treatment of infectious syphilitic mothers during pregnancy as compared with 15 per cent of failure by intensive arsenotherapy which was reported in the literature by Goodwin and Moore.[1b]

CONCLUSIONS

1. Penicillin may be administered to the pregnant syphilitic woman with safety to both her and the fetus.

2. Of the various drugs which are used in the intensive forms of treatment and which are designed to prevent prenatal syphilis, penicillin is unexcelled.

3. Failure to eradicate the disease in the mother by treatment with penicillin is not inevitably attended by the birth of a child in whom congenital syphilis develops, even though the mother's relapse occurs a few weeks after delivery.

NOTE.—By July 15, 1947, when the proof was being read, a total of 81 infants delivered of women treated with penicillin for early infectious syphilis during pregnancy had been observed. Except for the 1 stillborn infant mentioned previously, the remaining 80 infants were free of infection to date. This would reduce our rate of failure with penicillin therapy from 2.8 to 1.24 per cent.

CUTANEOUS DIPHTHERIA

Report of Ten Cases

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PERUSAL of the domestic and foreign literature indicates that the apparent increase of cutaneous diphtheria during and after the recent conflict closely parallels the trend observed in World War I.[1] While the disease is rather unusual among civilians, it occurs with some frequency among armed forces. The majority of reports deal with tropical and subtropical occurrence. With the return of large numbers of troops from areas where diphtheria is much commoner than in the United States, the possibility of cutaneous lesions should be kept in mind.

During a recent epidemic of diphtheria among American troops in Germany, 10 patients with cutaneous diphtheria were observed and treated. It is believed that their cases are of interest because of diagnostic difficulties due to the great variety of lesions and their location.

REPORT OF CASES

CASE 1.—G. J. P., a man aged 20, was hospitalized elsewhere on Dec. 7, 1945 with a history of "athlete's foot" of three weeks' duration. On December 15 he was transferred to the Ninety-Seventh General Hospital. Bilateral dermatophytosis was present. There was a large fissure between the third and fourth toes of the right foot, extending approximately 0.5 cm. over the dorsum of the foot. A purulent exudate covered this lesion. On December 17 a "dirty membrane" over the fissure was observed. A culture was taken at this time and reported positive for Corynebacterium diphtheriae on December 20, whereupon 100,000 units of diphtheria antitoxin was administered. Penicillin was administered intramuscularly during the next five days. Cultures from the lesion on December 20, 21 and 24 and Jan. 12, 1946 were reported positive for C. diphtheriae. The membrane disappeared within seventy-two hours after the administration of the antitoxin, revealing the presence of a deep ulcer. The lesion presented an undermined edge and a clean base of a vivid red color and was not particularly painful. The

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1. Saffron, M. H.: Cutaneous Diphtheria as a Military Problem, Arch. Dermat. & Syph. **51**:337 (May) 1945.

lesion filled in slowly and healed completely within the period of a month. Electrocardiographic tracings taken two weeks after the administration of the antitoxin revealed a diphasic T wave in lead IV, prominent Q waves in leads II and III and elevated S-T intervals in leads II and III. These changes reverted to normal two weeks later. Throat cultures became positive for C. diphtheriae on January 28 and did not become negative until March 1. The patient was discharged to duty on March 17 after one hundred days of hospitalization.

CASE 2.—T. M. B., a white woman aged 23, was hospitalized on Dec. 14, 1945 with the diagnosis of "contact dermatitis" of both hands. She was a nurse working in the ward of contagious diseases and there came in contact with cases of nasopharyngeal diphtheria. She gave a history of hay fever and an attack of contact dermatitis one year previously. On admission the palms revealed deep linear ulcerations in the region of the natural creases. The hands were erythematous, and the palmar surfaces of the fingers showed scaling. Therapy consisted of soaking the hands in solution of potassium permanganate and intramuscular

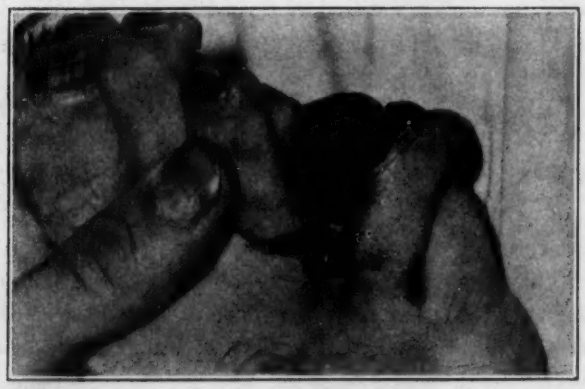

Fig. 1 (case 1).—Cutaneous diphtheria of the toe web (approximate duration, eight weeks; diphtheria antitoxin administered three weeks previously).

injections of penicillin. Despite this treatment the eruption became much worse. Decided edema of the hands and difficulty in flexing the fingers were noted. Numerous pustules developed on both hands. On December 27 cultures were reported positive for C. diphtheriae. On this date the patient received 100,000 units of diphtheria antitoxin after being desensitized. The improvement thereafter was dramatic. In forty-eight hours many of the pustules and the edema had disappeared. After exfoliation the underlying skin was pink, supple and healthy in appearance. The subsequent course was complicated by severe serum sickness and recurring secondary infections of the hands. Nose and throat cultures were negative on two occasions. The patient was evacuated to the United States on Feb. 15, 1946. The total time of hospitalization at this installation was sixty days.

CASE 3.—J. J. F., a white man aged 18, was admitted on Dec. 12, 1945 because of tinea cruris. Physical examination further revealed a small ulcerated area of the dorsum of the left foot near the base of the third and fourth toes. Local therapy consisted of soaking the affected parts in solution of potassium permanganate with good response of the crural lesion. However, on December 17 the lesion on the foot was noted to be "expanding." It presented a shallow ulcer

with sharp edges and a purulent base 0.5 cm. in diameter. On December 24 a culture from this lesion was reported as positive for C. diphtheriae. The patient was immediately given 1000,000 units of diphtheria antitoxin. He was also given sulfadiazine by mouth. The lesion healed slowly. A culture of the throat on Jan. 15, 1946 was positive for C. diphtheriae, but subsequent cultures failed to disclose the presence of the organism. Electrocardiographic tracings were normal. The patient was discharged to duty on January 31 after forty-nine days of hospitalization.

CASE 4.—A. L. L., a white man aged 27, was admitted on Dec. 15, 1945 because of acute severe dermatophytosis of both feet. Over the dorsum of the

Fig. 2 (case 5).—Cutaneous diphtheria of the left genitocrural area (approximate duration, seven weeks; diphtheria antitoxin administered four weeks previously).

right foot at the base of the second and third toes was an ulcer with undermined edges of a dirty necrotic base. There was little improvement after bed rest and soaking the feet in solution of potassium permanganate. On December 31 a culture was positive for C. diphtheriae (reaction to the virulence test was positive), and the patient received 100,000 units of diphtheria antitoxin. The purulent discharge disappeared rapidly, and on Jan. 3, 1946 a clean ulcer with undermined edges, 1 by 0.5 cm., could be seen in the aforementioned area. The lesion healed slowly. Nose and throat cultures were consistently negative for C. diphtheriae. Serial electrocardiographic tracings were normal. The patient was discharged to duty on February 5 after fifty-two days of hospitalization.

CASE 5.—R. B. B., a white man aged 29, was hospitalized elsewhere on Nov. 25, 1945 because of a lesion in the left inguinal region, which was thought to be secondary to scabies. In this area there was considerable erythema and excoriation, and in its center was a shallow ulcer approximately 2 cm. in diameter. The lesion became worse despite local therapy and intensive administration of penicillin. On December 11 a direct smear revealed "numerous bacilli resembling C. diphtheriae." The patient was given 70,000 units of diphtheria antitoxin. The following day a thick white membrane was removed from the base of the ulcer. On December 14 the base of the ulcer seemed to be much cleaner, and extension of the ulcer seemed arrested. On December 16 the patient was transferred to this installation. On the inner aspect of the upper part of the thigh was a shallow ulcer 5 cm. in diameter. The margins were sharp, and the base was covered by a purulent exudate. Cultures from the ulcer were positive for C. diphtheriae on December 16 and on Jan. 12, 1946. The reaction to the virulence test performed on the first culture was positive. The culture and the smear for Hemophilus ducreyi were negative. The Kahn reaction was negative. Further

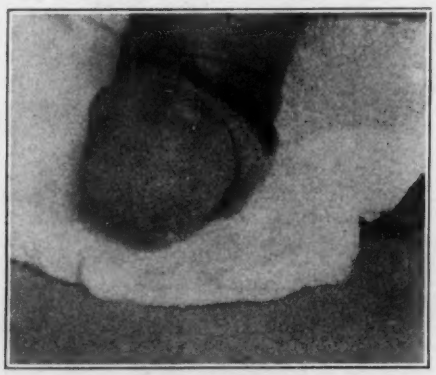

Fig. 3 (case 6).—Cutaneous diphtheria of the penis (approximate duration, seven weeks; diphtheria antitoxin administered one week previously).

therapy consisted of parenteral and local administration of penicillin. The lesion healed slowly. Repeated nose and throat cultures were negative for C. diphtheriae. Serial electrocardiographic tracings were normal. The patient was discharged to duty on February 11 after a total of seventy-eight days of hospitalization.

CASE 6.—S. J. H., a white man aged 26, was admitted to the Ninety-Seventh General Hospital on Dec. 17, 1945 because of a penile ulcer. The patient stated that after sexual intercourse on Nov. 24, 1945 he noted a laceration of the frenulum. Prior to admission two dark field examinations were negative for Treponema pallidum. A Kahn reaction was also negative. Physical examination revealed edema of the foreskin with paraphimosis. A large dirty ulcer extending almost completely around the shaft of the penis was present in the region of the coronal sulcus. Dark field examinations remained negative for T. pallidum. The Kahn reaction was negative on three occasions. Improvement was not noted after the administration of sulfadiazine by mouth and after local wet dressings. On Jan. 5, 1946 a positive culture for C. diphtheriae was reported, and the patient was given 100,000 units of diphtheria antitoxin. Penicillin therapy was started

on this date and continued for five days. The ulcer filled in slowly, and the edema disappeared. Electrocardiographic tracings revealed the T waves to be somewhat flat initially, regaining normal amplitude one month later. Nose and throat cultures were consistently negative for C. diphtheriae. The patient was discharged to duty on March 3 after seventy-six days of hospitalization.

CASE 7.—G. A. M., a white man aged 37, was hospitalized on Jan. 12, 1946 with a history of having been treated for dermatophytosis of the hands and feet

Fig. 4 (case 7).—Cutaneous diphtheria of the legs, hands and wrists (approximate duration, three months; picture taken immediately prior to the administration of diphtheria antitoxin).

since October 1945. In the twelve days prior to admission the eruption had become considerably aggravated. The lower half of both legs presented decided impetiginous lesions. The hands presented extensive exfoliation, especially of both palms, with impetiginous lesions on both wrists (fig. 4). Improvement was not noted after local application of solution of aluminum acetate, N. F. Cultures from the lesions of the hands were positive for C. diphtheriae on January 26 and 28. One hundred thousand units of diphtheria antitoxin was administered on

January 26. Improvement of the lesions of both the hands and feet was rapid. Within seventy-two hours the purulent exudate disappeared, and the skin beneath the exfoliations was observed to be pink and healthy. Improvement thereafter was sustained. Nose and throat cultures were persistently negative for C. diphtheriae. Serial electrocardiographic tracings were normal. The patient was discharged to duty on March 3 after forty-eight days of hospitalization.

CASE 8.—W. V. G., a white man aged 25, was hospitalized elsewhere on Feb. 8, 1946 because of "sores on the penis." The physical examination revealed multiple punched-out ulcers on the penile shaft, scrotum and perineum and in the pubic region. Repeated dark field examinations were negative for T. pallidum. The Kahn reaction was less than 10 units. A culture from the penile lesions was positive for C. diphtheriae (reaction to the virulence test was positive), and the patient received 60,000 units of diphtheria antitoxin on February 12. Intensive penicillin therapy was also administered during the next seven days. A culture taken on February 16 was again reported positive, and two days later another 60,000 units of diphtheria antitoxin was administered. At this time great improvement of the lesions was noted. On February 24 a third culture was positive for C. diphtheriae, and an additional 60,000 units of diphtheria antitoxin was administered. The lesions healed satisfactorily, but persistently positive nose and throat cultures prompted the patient's transfer to the Ninety-Seventh General Hospital on March 6. On admission healed lesions of the genital area were present. They were erythematous, slightly scaling and not indurated, and each measured approximately 0.5 cm. in diameter. There were one lesion of the pubic area, four of the right hemiscrotum and four of the shaft and foreskin of the penis. The time required for healing of these lesions was approximately twenty-six days.

The following 2 patients were briefly observed while in transit. They were being returned to the United States because of complications following cutaneous diphtheria.

CASE 9.—J. K., a white man aged 23, was hospitalized elsewhere on March 6, 1946 with pustular lesions of the legs and lower part of the abdomen, which were thought to be due to secondarily infected scabies. Intramuscular administration of penicillin and local therapy resulted in improvement of all the lesions except an ulcer in the right inguinal region. This ulcer measured 1 by 2.5 cm. and was described as being covered by a thin grayish membrane. On March 19 a culture from the ulcer was reported positive for C. diphtheriae. After the administration of 80,000 units of diphtheria antitoxin the ulcer healed slowly, leaving a nonpigmented atrophic scar. On March 24 the patient began to complain of difficulty in swallowing and of inability to read. These symptoms disappeared within three days while, simultaneously, weakness of all extremities appeared. Definite decrease in the tendon reflexes was present. A slow recovery of strength took place over a period of sixty days, during which time the patient received physical therapy and thiamine hydrochloride intramuscularly. Serial electrocardiographic tracings were normal.

CASE 10.—A. L. L., a white man aged 19, was hospitalized elsewhere on March 15, 1946 because of "eczema" of both arms. By March 22 improvement had not been noted, and ulcers were observed on both forearms. Cultures taken from two separate ulcers were reported positive for C. diphtheriae on March 24, whereupon 100,000 units of diphtheria antitoxin was administered. The lesions

healed slowly, leaving small atrophic scars. Serial electrocardiographic tracings revealed a decided depression of the QRS complex and the T wave in all leads. Considerable improvement occurred after five weeks of absolute bed rest.

SUMMARY

Ten cases of cutaneous diphtheria are reported. The lesions presented a diversified appearance and occurred on the extremities, the lower part of the abdomen and the genitalia. Diphtheria antitoxin was administered intramuscularly to all patients. In addition, some of the patients received nonspecific chemotherapy (penicillin, sulfadiazine and thiamine hydrochloride). Local nonspecific therapy was also employed. All patients required lengthy hospitalization. Electrocardiographic evidence of myocardial damage and peripheral neuritis was encountered. Throat cultures were positive for Corynebacterium diphtheriae in 3 cases.

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CUTANEOUS DISEASES IN ARMY AIR FORCE PERSONNEL

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THE TYPE of dermatologic cases encountered in the Army differ somewhat from those seen in civilian practice. This is due to the fact that most of the chronic, serious or extensive cutaneous disorders are disqualifying for military service. In the Army, since it is composed mainly of healthly young men, one encounters mostly acute cutaneous diseases acquired after induction. This is especially true in the Army Air Forces, since the physical requirements for flying are so strict as to eliminate most cutaneous diseases.

The conditions of army life in training and combat make certain diseases of the skin commoner than in civilian life. Such is the case of scabies, dermatophytosis and dermatitis solaris. When one excludes the tropical diseases of the skin and the cutaneous diseases prevalent in tropical regions, which may be acquired by all types of personnel stationed in those areas, the incidence and the nature of different cutaneous disorders vary somewhat in each branch of the service.

The environment, the nature of duties, the instruments and the materials handled vary considerably in the ground forces, navy and air forces. In addition each individual assignment will bring personnel in contact with substances not used in another type of duty. All these factors will play a role in the production and persistence of cutaneous diseases. The substances or materials handled may lead to dermatitis venenata or may aggravate, by mechanical irritation or sensitivity, preexisting dermatoses. For these reasons the cutaneous diseases commonly encountered in the personnel of a destroyer, as shown by E. C. Kley,[1] will differ from those of a chemical warfare unit or a high altitude combat crew.

Some diseases are of greater importance in one branch of the service than in another, depending on the location of the disease and the type of duty of the patient. Such is the case in verruca plantaris and mild dermatophytosis, which may be incapacitating in a member of the infantry while they will be of minor importance in a navigator or a bombardier.

This study was made while the author was serving in the Medical Corps, Army Air Forces, Army of the United States.

1. Kley, E. C.: Skin Diseases Aboard a Destroyer, U. S. Nav. M. Bull. **42**: 407 (Feb.) 1944.

In Army Air Forces personnel the type, incidence and importance of cutaneous diseases vary according to the assignment of the soldier. The causes of contact dermatitis of a gunner will differ from those of the disease in a pilot. A thorough knowledge of their duties and of the substances they handle is a great asset in the proper management of dermatologic cases. This refers not only to dermatitis venenata but to other cutaneous diseases as well.

Other factors which may possibly play a role in cutaneous diseases in air force personnel are physiologic changes occurrring at high altitude, such as aeroembolism, and sudden extreme changes of temperature. Little is known of the importance of these factors, since practically no research has been made on these problems from the dermatologic standpoint. The expected greater development of aviation in the postwar period makes this an interesting new field for research.

This paper is intended to summarize the experience gained by me in two years as chief of the dermatologic sections at two large air bases in the Southwest, one of them a regional hospital. These bases were engaged in training combat crews for heavy bombers. The dermatologic section consisted mainly of a large outpatient clinic. Patients requiring hospitalization were treated in the ward. In this paper a discussion will be made successively of the present knowledge of the physiologic changes of the skin in flight, the incidence of cutaneous diseases at the dermatologic clinic and the diseases of special importance in air force personnel.

PHYSIOLOGIC EFFECTS OF FLYING ON THE SKIN

In spite of the great and rapid advances of aviation medicine, little has been written on the physiologic effects of flight on normal and pathologic skin. Only occasional references to cutaneous changes are found in the literature. Most of these notes are brief, since they have been made during the study of other organs.

From the standpoint of cutaneous diseases, the most important changes encountered in flight are the variations of barometric pressure and the sudden changes of temperature. One of the main effects of changes in pressure on the human body is aeroembolism (decompression sickness and bends). This is characterized by the formation of nitrogen bubbles in the body tissues and fluids. It is due to the fact that in rapid ascent to high altitudes the amount of dissolved nitrogen in the body is in excess of that which can be held in solution. When the ascent is rapid to altitudes of 30,000 feet or more, the nitrogen gas will tend to come out of solution and form bubbles not only in the blood but in other tissues as well. Different factors are important in the production of aeroembolism, such as the rate of ascent, altitude attained, time the person

remains at altitude, individual susceptibility, environmental temperature, vascularity of the tissues and rate of blood flow. The more rapid the climb, the sooner the symptoms appear. At less than 30,000 feet (9,144 meters) they are rare, but at higher altitude they develop easily. The joints and the cerebrospinal, cardiovascular and the respiratory systems are affected. Tissues with a high content of fat are more prone to the formation of bubbles.

The skin plays an important role in aeroembolism. According to Armstrong,[2] cutanous manifestations are secondary in frequency only to pains in the joints. There may be peripheral neuritis affecting the nerve endings. In such cases there is associated dermatitis with intense itching and burning of the skin of the area supplied by the nerve. This persists for several days. There may be macular eruptions or urticarial lesions covering the whole abdomen. Armstrong concluded that it would appear that the mechanical irritation of the gas bubbles on the posterior horn cells of the spinal cord may offer a clue to some of the neurodermal conditions whose causes are yet more or less obscure.

Other cutaneous manifestations of aeroembolism may be sensations of cold and heat, generalized tingling or formication. The last has been compared to "colonies of ants rushing madly over the surface of the body." It is likely that all these symptoms are due to nitrogen bubbles in the skin or fat of the subcutaneous tissue or of the nerve endings. Another factor which may affect the skin of a flyer is sudden changes of extreme temperature. In summer in the Southwest the average temperature inside a plane on the ground is 120 F. (49 C.). Shortly after a rapid ascent to an altitude of 30,000 feet the temperature averages —47 F. (—44 C.). To cope with these extreme changes closed cabins and specially made protective clothing are used.

The role of the skin in the regulation of the body temperature through perspiration and vasoconstriction is well known. Extreme cold temperatures may lead to frostbite. Its effect in aviation personnel has been reported.[3] Decreased tactile efficiency due to extreme cold has been observed. The effect of these sudden changes of temperature on normal and pathologic skin has not been determined. It seems reasonable to surmise that frequent repetition of these abnormal conditions will affect the cutaneous texture.

There are some chemical changes of the blood occurring at high altitude which may be important to the physiopathologic changes of the

2. Armstrong, H. G.: Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939, p. 340.

3, Sheeley, W. F.: Frostbite: Eighth Air Force, Air Surgeon's Bull. **2**:23 (Jan.) 1945.

skin repeatedly exposed to such conditions. Burrill and colleagues [4] showed that exposure to 18,000 feet (5,486 meters) caused a temporary rise in the excretion of sodium, potassium and chlorides.

Undoubtedly the skin plays a role in this process, since it is one of the greatest reservoirs of chloride. The possible changes of the blood cholesterol at low barometric pressure were investigated by Muller and Talbott,[5] with negative results. However, Schemenky [6] found increased values following exposure to high altitude. The importance that this fact may have in dyslipidosis remains to be determined.

With the purpose of ascertaining the effect of flying on different cutaneous diseases, patients on flying status were always questioned about the effect of flying on the condition of their skin. This, although wholly inadequate to make definite statements, gives a hint on the reaction of cutaneous diseases to flying conditions. The result obtained by such inquiry showed that most diseases of the skin are not appreciably affected by flying at high altitude. Occasionally pruritus was exacerbated. This was frequently the case in pruritus ani, pomphyolyx, dermatophytids and similar eruptions. It is impossible to determine to what extent the nervous tension associated with flying or the sudden changes of temperature may have had in the appearance or aggravation of pruritus.

In summary it can be said that there is surprisingly little information on the physiopathologic changes of the skin exposed repeatedly to flying at high altitude. There is a great need for research to clarify many obscure points on this subject. These studies should be made by qualified personnel, it being kept in mind that the skin is an important functioning organ and not merely a passive membrane structure.

STATISTICAL DATA

The dermatologic clinic was operated as part of the medical service. The data here given include material from two stations—one, a station hospital, in which the skin clinic was operated for nine months, and the other, a regional hospital, where the clinic functioned for thirteen months. The clinic of the latter was larger, averaging 16 military patients daily. The total number of patients seen was 2,327. The total number of visits per patient was 4.2. With the purpose of decreasing the noneffectiveness of cutaneous diseases and preventing the interruptions of training as much as possible, hospitalization was kept to a minimum. At the

4. Burrill, M. W.; Freeman, S., and Ivy, A. C.: Sodium, Potassium and Chloride Excretion of Human Subjects Exposed to Simulated Altitude of Eighteen Thousand Feet, J. Biol. Chem. **157**:297 (Jan.) 1945.

5. Muller, G. L., and Talbott, J. H.: The Effect of High Altitudes on Cholesterol, Lecithin and Fatty Acids in the Plasma of Healthy Men, Arch. Int. Med. **47**:855 (June) 1931.

6. Schemenky, cited by Muller and Talbott.[5]

regional hospital 6 to 8 patients were hospitalized monthly. At least half of these were transferred from satellite bases.

The ten commonest diseases of the skin encountered in air force personnel at the dermatologic clinic are shown in the table. Although most patients with cutaneous diseases were referred to the clinic by the station infirmary, where the patients reported on sick call, some patients with simple diseases were treated successfully there without the aid of dermatologic consultation. Therefore, the figures and percentages mentioned with each disease are intended only to give an idea of the incidence of the disease.

A study of the table will show that the most commonly observed disease was dermatitis venenata. In some instances this resulted from the application of strong ointments on acutely inflamed skin. In other cases it was due to overtreatment. In many instances the dermatitis resulted from contact with substances, materials and equipment handled

The Ten Commonest Diseases of the Skin Encountered in Air Force Personnel

	No. of Cases	Percentage
1. Dermatitis venenata	402	17.3
2. Pyodermas	352	15.1
3. Fungous infections and ids	206	8.4
4. Verrucae, all types	187	8.0
5. Urticaria, erythema toxicum	106	4.6
6. Dermatitis and eczemas	101	4.3
7. Neurodermatitis	96	4.1
8. Scabies	91	3.9
9. Acne vulgaris	88	3.8
10. Pompholyx-like eruptions	81	3.5

in the operations, repair or maintenance of aircraft. Pyodermas included deep, superficial and follicular pyogenic infections. Fungous infections, including dermatophytids, occupied only the third place, averaging 8 per cent of the total visits. Verruca vulgaris was the commonest type of wart seen. Verruca plantaris was decidedly rare. Dermatitis of unknown cause, eczema, scabies, acne and localized and generalized neurodermatitis were seen in approximately the same incidence. A peculiar superficial desquamation resembling dermatophytids or pompholyx was commonly seen. The dry and warm climate may have played a role in the production of this disease.

Among the rare diseases of the skin seen were scleroderma, tuberculids, dermatitis herpetiformis, erythema multiforme bullosum and lupus erythematosus. It is worthy of mention that no case of pediculosis corporis was seen and that pediculosis pubis was almost nonexistent.

CUTANEOUS DISEASES OF SPECIAL SIGNIFICANCE TO AIR FORCE PERSONNEL

Dermatitis Venenata.—Dermatitis venenata in personnel operating and repairing aircraft may be divided into two large groups: (*a*) derma-

titis produced by substances such as fluids, greases and solvents, with which personnel come in contact in the process of repair, maintenance and operation of airplanes and (*b*) dermatitis venenata produced by equipment or clothing used by flying personnel.

Dermatitis Venenata Produced by Substances Handled in the Repair, Maintenance and Operation of Aircrafts: This is most frequently encountered in ground crews, although it may be present in members of the flying personnel engaged in mechanical work, as engineers, or those handling irritants used in cleaning of their equipment, such as gunners. Civilians working in repair depots are subject to similar hazards. Fletcher Hall [7] found that zinc chromate is, by large, the commonest cause of dermatitis venenata in the aircraft industry. He demonstrated that the terms "dural poisoning" or "aluminum poisoning," commonly used by workers and physicians, are incorrect, since in only 5 per cent of his cases were the conditions found to be due to dural and in only 2 per cent to aluminum. In 65 per cent zinc chromate was responsible for the dermatitis.

A good knowledge of the chemical nature of the substances used by the personnel engaged in repair and maintenance of airplanes is essential for the proper management of patients with dermatitis venenata. For instance, a gunner in his routine work handles a certain number of lubricating oils and cleaners which differ from those used by engineers or ground crew mechanics.

Armstrong [8] classified the primary irritants encountered in the repair and maintenance of aircrafts into six groups: (1) dopes, paints and related materials; (2) cleaning materials; (3) fire-extinguishing compounds; (4) engine exhaust gases; (5) aviation gasoline, and (6) hot oil fumes. Only some of those are important from the dermatologic standpoint. A complete list of the potentially irritating substances handled by ground crews and flying personnel is not within the scope of this article. Only the most important ones will be discussed here. Among the substances handled by air force personnel which are known to be irritants to the skin are (1) carbon tetrachloride (used as cleaning fluid to clean parts of engines, propellers, radar, bombsights, parachute harnesses and other materials; it is also used as a fire extinguisher); (2) ethylene dichloride (used for removal of carbon, as fuel cell repair and as paint remover); (3) trichloroethylene (used as a degreaser); (4) benzine (also used as a degreaser); (5) toluene (employed as thinner, dope and degreaser), and (6) aviation gasoline. The last is a complex fluid containing tetraethyl lead and xylidin.

7. Hall, A. F.: Occupational Contact Dermatitis Among Aircraft Workers, J. A. M. A. **125**:179 (May 20) 1944.

8. Armstrong,[2] p. 166.

Tetraethyl lead is an irritant to the skin and also produces systemic symptoms. Xylidin is highly toxic when absorbed through the skin.[9]

Dermatitis may be produced by large quantities of any of the primary irritants aforementioned. Small amounts of any of the solvents used may bring forth a dermatitis if a patient is hypersensitive to that particular substance.

Dermatitis Venenata Produced by Equipment or Clothing Used by Flying Personnel: Flying personnel are required to wear special clothing and equipment during operation. Heavy clothing is issued to protect them against cold temperatures. Different materials, varying from nylon to wool, come in contact with their skin, all of them being capable of irritation.

Another source of contact dermatitis is the rubber of earphones, goggles, throat microphones and oxygen masks. Cases of dermatitis venenata produced by those devices are not uncommon. In one of my cases dermatitis venenata developed every time the skin of the neck of a patient came in contact with the Bakelite disks of the throat microphone. This was proved by patch tests.

Sycosis Vulgaris.—Sycosis vulgaris is of much greater importance in the air force than in ground forces or in civilian practice. In the last two it is mainly of cosmetic interest. In flying personnel lesions of sycosis vulgaris may interfere with the proper fitting of devices essential to flying at high altitude, such as oxygen mask or throat microphones. Any disease of the skin which will hamper the proper fitting of these devices will handicap the efficiency of a flier. In cases of severe conditions it may prevent their use, thus incapacitating the patient in the performance of his duties or interrupting the training of qualified personnel.

The aggravating effect of dermatitis venenata due to rubber of oxygen masks and rubber and Bakelite of the throat microphones, together with the irritating action of the solutions used to clean these devices should be kept in mind. The mechanical action of friction associated with perspiration should also be taken into consideration as a possible cause of exacerbation. Occasionally, grounding a patient for one or two weeks has a beneficial effect. Special attention should be paid to the treatment of this disease in the early stages. Penicillin locally [10] and roentgen therapy usually gave satisfactory results.

Acne Vulgaris.—For the same reasons mentioned in the discussion of sycosis vulgaris, severe acne is a common cause of disability in flying personnel. The continuous friction and pressure exercised by oxygen

9. Parrish, H. C., and Byram, D. H.: Industrial Solvents in the AAF, Air Surgeon's Bull. **2**:195 (July) 1945.

10. Canizares, O.: Penicillin in Dermatology: A Study of One Hundred and Seventy-Four Cases, Arch. Dermat. & Syph. **54**:19 (July) 1946.

masks and throat microphones are an important source of irritation on chin, neck and about the mouth. The warm dry climate of the geographic area where this study was made seems to have beneficial effect on acne by decreasing the activity of the sebaceous glands and thus reducing the oiliness of the skin. However, on many occasions, severe eruptions with cystic lesions were encountered, making flying personnel unfit for duty.

Dermatophytosis.—Fungous infection of the feet was commonly seen, especially in summer. The mild intertriginous form was the type most frequently observed. Since the type of activities of air force personnel does not require too strenuous exercises or long marches, hospitalization was successfully kept at a minimum and reserved for severe conditions complicated by secondary infection.

Tinea Cruris.—Tinea cruris was rather common in flying personnel. It was often aggravated by friction of the lower straps of the parachute harness. Grounding a patient for a few days was found to be a great help to the local treatment.

Verruca Plantaris.—Verruca plantaris was observed only rarely. Its incapacitating nature is minimal, except possibly in some pilots. In them the disease may handicap the steady pressure on pedals required for the control of some types of planes.

Miscellaneous Diseases.—Pruritus ani was rather frequently the cause of disability. The nervous tension associated with flying, together with the long hours sitting required on long missions, made this disease a major problem in some cases. Dermatophytids, dyshidrosis and hyperhidrosis may be a handicap in combat crews, as they may hamper the efficiency of a bombardier or a gunner at the precise moment when it is most needed. Here too, the nervous tension of flying or combat may play an aggravating role. Painful nodules of the ear were occasionally seen. The mechanical irritation of earphones may have contributed to their formation.

SUMMARY AND CONCLUSIONS

1. Dermatologic problems encountered in Army Air Forces personnel are discussed. The study covers a period of two years and was made at the skin clinic of two large air bases in the Southwest, one of them a regional hospital. A total of 2,327 patients was seen.

2. The ten diseases of the skin most commonly seen are presented. The first three were dermatitis venenata, pyogenic infections and fungous infections.

3. The diseases of special significance to air force personnel are discussed. The importance of dermatitis venenata is stressed. It may be produced by substances, materials or equipment handled during the

operation, repair or maintenance of aircraft. Sycosis vulgaris and acne are of importance in flying personnel. Dermatophytosis is seldom incapacitating.

4. There is surprising little information on the physiopathologic changes of the skin exposed repeatedly to flying at high altitude. There is great need for research in this field.

5. The importance of cutaneous disease in air force personnel varies according to its location and assignment of the patient. A thorough knowledge of his duties, the substances, materials and equipment he handles in his work is a great asset in the proper management of dermatologic patients.

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AMINOPHYLLINE AS AN ANTIPRURITIC AGENT

II. Intramuscular Injection

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A GENERAL report on the use of theophylline ethylenediamine (aminophylline) by injection as an antipruritic agent was presented in a previous paper.[1] It was demonstrated that this agent was most effective when administered intravenously. However, when the drug was given by this route, disconcerting immediate reactions, and even possible fatal reactions, limited its value in dermatology. The evanescence of the relief also indicated that further studies were necessary to make its use practical. The present report concerns the results obtained in 17 patients suffering with various itching dermatoses who were treated with intramuscular injections of aminophylline.

MATERIAL

Seventeen patients were studied. The table briefly outlines the salient features in each instance. Thirteen patients were women, and 4 were men. All but 2 were white, and the others were Negro. The ages ranged from 31 to 71 years, roughly two thirds being between the ages of 41 and 60 years. In all instances the itching had resisted conventional antipruritic measures, including roentgen ray therapy in many. The diagnoses included many of the more resistant pruritic diseases. The dosage employed for all patients was 0.5 Gm. of aminophylline administered intragluteally in 2 cc. of fluid.

RESULTS

In 7 patients the relief of itching was dramatic. The pruritus usually ceased within thirty to forty-five minutes and did not recur until twelve to thirty-six hours later. In 1 patient, a woman with eczema of the hands (case 7), one injection completely relieved all itching for a period of six days. This patient had failed to respond to treatment with the usual antipruritic agents over a period of one month.

Two patients, 1 with contact dermatitis due to vegetation (case 3) and 1 who had dermatitis due to dye in clothing (case 13), experi-

1. Epstein, E.: Theophylline Ethylenediamine as an Antipruritic Agent: Preliminary Report, Arch. Dermat. & Syph. **53**:281 (March) 1946.

enced great relief, and in both instances injections quickly controlled recurrences.

However, the over-all results were not so successful in some of the other patients, who experienced temporary relief. Some needed daily injections to control the itching, and even then they failed to get well. This is exemplified by the response in the patient (case 16) who received nine daily injections for pruritus vulvae and pruritus ani and the patient (case 6) who was given seven injections for pruritus vulvae. While both were relieved by the injections, the itching promptly recurred as the effect of the treatment wore off.

Outline of Cases Studied and Results Obtained in Seventeen Patients Treated with the Intramuscular Injection of Aminophylline

Case	Age	Sex	Diagnosis	Number of Injections	Amount of Relief	Reactions
1	49	M	Generalized eczema	1	Little	Local
2	52	M	Generalized dermatitis due to cement	3	None	Local
3	36	F	Generalized dermatitis due to plants	17	Very decided	Local; nausea
4	50	F	Pruritus following scabies....	1	Patient failed to return	
5	46	F	Dermatitis of the arms and chest due to poison oak	2	Decided	Local
6	46	F	Pruritus vulvae	7	Decided	Local
7	41	F	Eczema of the hands.....	2	Very decided	Local
8	31	F	Chronic urticaria	1	None	Local
9	42	F	Contact dermatitis of the face	1	Some	Very severe local
10	71	M	Generalized eczema due to plants	1	Little	Local
11	56	F	Dermatitis venenata of the neck and chest	1	Moderate	Local; nausea
12	34	F	Dermatitis of the hands due to plants	17	Decided	Local
13	42	F	Dermatitis of the axillas due to dyes	6	Very decided	Local; menstruation
14	62	F	Generalized pruritus	2	None	Local; general shock
15	43	F	Generalized toxic dermatitis..	1	None	Local; nausea
16	64	F	Pruritus ani and pruritus vulvae	9	Decided	Local
17	56	M	Generalized dermatitis due to cement	2	Moderate	Local

Six patients were sure that they experienced little or no benefit from the injections. In 3, only mild results were obtained. One patient (case 4) did not return for further observation.

REACTIONS

Aminophylline, as it is furnished for intramuscular injection, is in an alkaline solution. According to Kemp,[2] the addition of acid solutions of local anesthetics results in precipitation of their alkaloids. Therefore they cannot be added to the solution of aminophylline. Unfortunately, reactions to the injections are often painful. Variations of site and depth of the injection, as well as massage and exercise, did not help to alleviate pain, which occurred in all patients, but not on all

2. Kemp, R. S.: Personal communication to the author.

injections. The patients usually complained of numbness and stiffness of the leg immediately or at any time up to thirty minutes after the injection. Many of the patients required assistance in order to leave the office after the injection because of what they described as a "paralysis" of the leg. This often lasted for several hours. Soreness might persist for days. There was no formation of nodules.

Despite the usual precautions in aspiration, apparently a small amount of the concentrated solution entered the blood stream in 1 patient (case 14). This resulted in symptoms of shock. The patient became weak and cold. The pulse was imperceptible, and hypotension developed. A feeling of impending death ensued. The patient was not sufficiently recovered to leave the office for an hour.

Several patients complained of nausea after the injection. One insisted that she started to menstruate within fifteen minutes after each of the six injections that she received (case 13). No pregnant women were treated with this agent.

COMMENT

Aminophylline, injected intravenously or intramuscularly, is an effective antipruritic agent. However, its toxicity and the short duration of its effect make one hesitate to use it intravenously. The high frequency of reactions prevents its full use intramuscularly. Four patients, all of whom had been undergoing treatment for some time, failed to return after one or more painful reactions to injections of aminophylline.

From this report it can be seen that the methods thus far suggested are impractical for the routine use of aminophylline as an antipruritic agent.

Some work has been done on administering the dose of 0.5 Gm. of aminophylline in 1,000 cc. of solution of dextrose or isotonic solution of sodium chloride. The therapeutic results have not been satisfactory, but the toxicity, both immediate and delayed, has apparently been eliminated. It is possible that the dose of aminophylline could be given intravenously in 100 to 500 cc. of solution with safety and efficacy.

SUMMARY

Seventeen patients with various severe itching dermatoses were treated with the intramuscular injection of 0.5 Gm. of aminophylline in 2 cc. of solution. In 7 patients the relief of itching was dramatic. However, the local and general reactions were so severe as to prevent the general use of this drug as an antipruritic agent.

The material used in this study was furnished by G. D. Searle & Co.

COMEDOS LOCALIZED IN THE TEMPOROZYGOMATIC AREA

CHRISTOPHER DOUCAS, M.D.
ATHENS, GREECE

TOWARD the end of 1944 and during 1945, 15 patients with an unusual eruption consisting of numerous comedos localized in temporozygomatic areas were seen by me in the outpatient department of the Evangelismos hospital. Such an eruption has not been described previously in our literature or in foreign literature.

Almost the same clinical picture was presented in all cases. This eruption was seen in 1 man; all the other patients were housewives between the ages of 25 and 60. The eruption consisted of symmetric patches of numerous small comedos localized in the temporal areas, extending from the ends of the eyebrows to the zygomatic bones and from the outer canthus of the eyes almost to the hair line. In 2 patients there was slight inflammation around the comedos. In 4 patients there was brownish pigmentation around the comedos, which resembled Riehl's melanosis. However, pigment was not seen in the corium on histologic examination. Comedos were not seen on the nose, cheeks, chin, chest or back except in 2 cases in which there were a few scattered comedos extending onto the cheeks.

A specific cause for such an eruption could not be determined, but many interdependent factors were suspected because of the abnormal living conditions that prevailed during the time this disease was observed. It was felt that the many dietary deficiencies and the substitutes prevalent during the war contributed to the appearance of the eruption in persons predisposed because of endocrinosympathetic disturbances, as occurs in Riehl's [1] melanosis.

Nervous tension was considered to be important in the production of the disease. Berès [2] said that nervous shock can provoke hyperkeratosis of the sebaceous glands, and all these patients were neurotic. They cried without reason, trembled and were continuously in a state of excitement since the onset of the eruption at the time of the riots in

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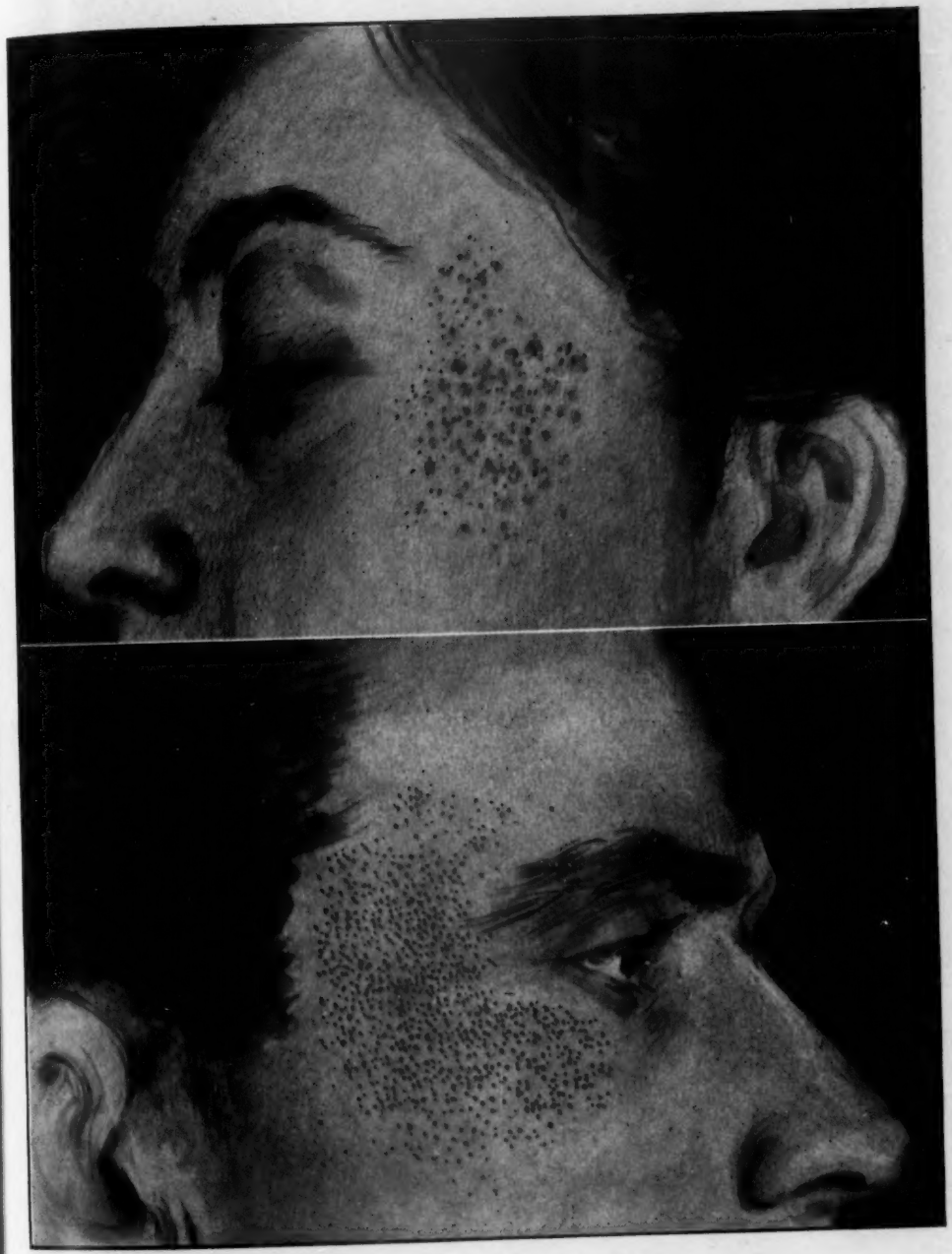
From the Department of Dermatologic and Venereal Diseases of the Evangelismos hospital, Athens, Greece.

1. Riehl: Ueber eine eigenartige Melanose, Wien. klin. Wchnschr. **30**:780 (June) 1917.

2. Berès, cited by Stannus.[4]



Comedos localized in the temporozygomatic area.

UNIV. OF MICH.

December 1944. Sex hormone balance was disturbed in most of the women during this time.

Substitute or inadequate foodstuffs may have been partially the cause of the eruption. Both wheat and fat substitutes were used during this period. Hyperkeratosis due to deficiency in vitamin A has been described by Frazier and Hu,[3] Stannus,[4] Sullivan and Evans.[5] Moult [6] and others said that deficiencies in vitamin B, C and E and in fatty acids provoked hyperkeratosis. These vitamins and fatty acids were lacking during the occupation of Greece.

The severe cold weather during December 1944 may have had some effect. Berès [2] stated that cold produces hyperkeratosis.

Since the eruption occurred primarily in women, the factor of the effect of the local use of cosmetics containing the substitute oil and ingredients obtainable during the war cannot be eliminated, although most of the women denied that they had used brilliantine, face cream or face powder. Garnier,[7] Gougerot [8] and Tzanck [9] reported such cases due to the use of brilliantine.

Histologic examination showed many keratinized cysts replacing the sebaceous glands. Some of the cysts were open on the surface, and others were closed beneath the epidermis. There was some atrophy of the hair follicles, and hairs were found below the cysts or even inside them. Hair was not found in other areas. There was flattening of the papillae and thinning of the prickle cell layer, and many of the cells were full of pigment. The granular layer was barely perceptible. The stratum corneum was normal. The blood vessels of the upper part of the corium were slightly dilated, and there was a little perivascular round cell infiltration. Demodex folliculorum was not found.

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3. Frazier, C N., and Hu, C.-K.: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507 (Sept.) 1931.

4. Stannus, H. S.: Vitamin A and the Skin, Proc. Roy. Soc. Med. **38**:337 (May) 1945.

5. Sullivan, M., and Evans, V.: Nutritional Dermatoses in the Rat: XI. Vitamin B Complex Deficiency, Arch. Dermat. & Syph. **51**:17 (Jan.) 1945.

6. Moult, F. H.: Histopathology of Rat Skin in Avitaminosis A, Arch. Dermat. & Syph. **47**:768 (June) 1943.

7. Garnier, G.: Boutons d'huile du visage par brillantine, Bull. Soc. franç. de dermat. et syph., March 3, 1944, no. 3-4, p. 84.

8. Gougerot, H.; Carteaud, A., and Grupper: "Epidemie" de comédons par les brillantines, crèmes etc., de guerre, Bull. Soc. franç. dermat. et syph. p. 286.

9. Tzanck, A.; Sidi, E., and Dobkevitch, S.: Nombreux cas d' éruption acnéiforme provoqués par une brillantine de fabrication récente, Bull. Soc. franç. de dermat. et syph., November-December 1945, no. 11-12, p. 293.

TREATMENT

Quick response to treatment was obtained by the use of a solution of 2 per cent resorcinol in alcohol combined with simple extraction of the comedos. There was not any relapse of the disease.

SUMMARY

Toward the end of 1944 and during 1945, 15 patients with comedos localized in the temporozygomatic areas and not accompanied by acne vulgaris or any evidence of inflammation were seen in the outpatient department of the Evangelismos hospital. Fourteen of the patients were neurotic women between the ages of 20 and 60 years, who manifested varying degrees of ovarian hormone disturbance. Most of the patients did not use brilliantine, face cream or face powder.

30 Stournara Street.

OTORHINOPHYMA, PRURITUS AND ALOPECIA TOTALIS SYNDROME

Response to Testosterone

SAMUEL AYRES Jr., M.D.
AND
ANKER K. JENSEN, M.D.
LOS ANGELES

THE PATIENT herein described presents a clinical picture which is unlike anything encountered in our experience and which, so far as we can determine, has not been described in available medical literature. At the time the patient was presented before the Los Angeles Dermatological Society over two years ago [1] no one who saw him had ever observed a similar case, and the majority of the physicians who discussed the case felt that it represented either some type of lymphoblastoma or some unusual clinical entity. After publication of this report, Dr. Norman Tobias, of St. Louis, in a personal communication,[2] expressed his interest in the case and stated that he had recently seen a patient who, he felt, presented an identical picture. More recently, Dr. Tobias, in reply to a brief questionnaire, indicated that his patient not only exhibited the same clinical characteristics but also responded in a similar manner to treatment.

While it is obviously imprudent to draw conclusions from a single case or, at best, from 2 cases, and while the good results of treatment obtained in these 2 cases might not be duplicated, yet the objective appearance and discomfort of our patient were so extraordinary and the therapeutic results were so dramatic that it seemed worth while to record the case in detail.

REPORT OF A CASE

A. R. L., an American-born white man aged 66, entered the Los Angeles County General Hospital on the dermatologic service Oct. 1, 1943 because of changes in the skin. The onset of the changes was about fifteen years before, when the patient

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From the Department of Dermatology and Syphilology of the Los Angeles County General Hospital.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 1946.

1. Ayres, S., Jr., and Jensen, A. K.: A Case for Diagnosis (Lymphoblastoma?), Arch. Dermat. & Syph. **49**:457 (June) 1944.

2. Tobias, N.: Personal communications to the authors.

began to lose his hair in patches. This loss of hair progressed for about five years, until he was totally devoid of hair, including eyelashes, eyebrows and body hair. This condition had persisted up to the time of his entering the hospital. Generalized itching had been present for a number of years, but a visible eruption had first become apparent about two and one-half years prior to admission. This had become more severe, with an accompanying inflammatory hypertrophy of the ears, nose, superciliary areas, chin and cheeks.

The patient stated he had lost the "pep" he used to have, but was not aware of any loss of weight.

Previous treatment had been carried out in a private clinic and had included various kinds of topical applications, low voltage roentgen ray therapy, ultraviolet irradiation, autohemotherapy, intravenous injections of strontium bromide, neoarsphenamine and various other drugs. No relief had been obtained.

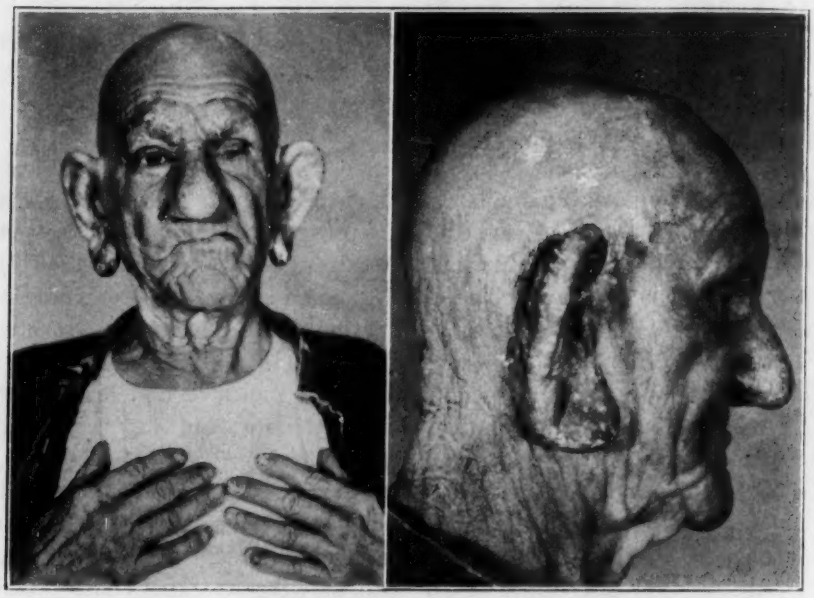

Fig. 1.—Condition prior to treatment with testosterone, showing alopecia totalis and peculiar hypertrophy of nose, ears and face.

Past History.—The patient had typhoid forty years before entering the hospital. He had not had venereal infections, allergic manifestations or recent illness. He had lived in Mexico between 1902 and 1909 in a mining camp. His left eye was removed twelve years before admission after an injury. His ears had been draining a sticky material for six months. There had been no significant cardiorespiratory or gastrointestinal abnormalities. He had experienced nocturia two or three times with difficulty in starting urination, but with no burning. He had severe arthritis in the left shoulder for four months.

Physical Examination.—The patient was a well developed, well nourished man, who appeared to be older than 66 years. He was suffering obvious discomfort from a pruritic eruption. Hair was totally absent from the scalp, face and body. No significant lymph nodes were observed. The face presented a striking appearance, with some diffuse puffing and pronounced hypertrophy associated with

redness, scaling and excoriations of superciliary areas, nose, chin, mouth and especially the ears. The nose was bulbous and almost twice the normal size. The ears were swollen to approximately twice their normal size, and there were a number of small ulcers and oozing in the region of the concha.

The facial appearance was so grotesque as to be suggestive of a gargoyle. The oddness of the patient's appearance was heightened by the glass eye on the left side. The vision in the right eye was fair, and the pupil reacted normally to light and acccommodation.

The skin elsewhere on the body was covered with small discrete maculopapules covered with crusts and excoriations and surrounded by an erythematous halo. These were most numerous on the legs with a few on the arms and trunk. The finger nails were atrophic and "warped." The heart, lungs and abdomen were normal.

Laboratory Data.—Hematologic studies made on Oct. 4, 1943 showed a hemoglobin level of 12.8 Gm. (80 per cent); red blood cells, 3,970,000; color index, 1.09;

Fig. 2.—Appearance nineteen months after oral administration of methyl testosterone for only four months, showing the growth of hair and subsidence of ears and nose.

white blood cells, 15,700 and reticulocytes, 0.8 per cent. The platelets were normal in number, toxic granulation was moderate, and there was slight anisocytosis. The differential count showed: neutrophils, 42 per cent; large lymphocytes, 20 per cent; small lymphocytes, 22 per cent; monocytes, 6 per cent; eosinophils, 3 per cent, and "blasts," 7 per cent. Comment by the hematologist: "This was compatible with a certain stage of Schilling type leukemia, but it is not impossible that this was a reactive blood."

Hematologic studies made on Nov. 10, 1943 showed a hemoglobin level of 12.16 Gm. (76 per cent); red blood cells, 3,560,000; color index, 1.15, and white blood cells, 21,050. The platelets appeared normal, and the red blood cells showed slight hyperchromasia. The differential count was as follows: neutrophils, 61 per cent; lymphocytes, 27 per cent; monocytes, 7 per cent, and eosinophils, 5 per cent. Comment by the hematologist: "There was no evidence of hematologic disorder, except that there was leukocytosis with absolute lymphocytosis."

Hematologic studies made on Nov. 20, 1943 showed a hemoglobin level of 10.4 Gm. (65 per cent); red blood cells, 3,560,000; color index, 0.96, and white blood cells, 16,150. The platelets and neutrophils appeared normal, and the red blood cells were slightly anisocytotic. The differential count was as follows: neutrophils, 60 per cent; lymphocytes, 26 per cent; monocytes, 7 per cent, and eosinophils, 7 per cent. Comment by the hematologist: "The blood showed moderate monochromic anemia and slight eosinophilia. There was nothing in the peripheral blood of a leukemic nature."

Hematologic studies made on Jan. 17, 1944 showed a hemoglobin level of 12.8 Gm. (80 per cent); red blood cells, 4,040,000; white blood cells, 9,850, and reticulocytes, 0.5 per cent. The platelets were normal in number, and there was slight anisocytosis. The differential count showed: neutrophils, 62 per cent; lymphocytes, 26 per cent; monocytes, 3 per cent; eosinophils, 8 per cent, and basophils, 1 per cent. Comment by the hematologist: "The blood was probably normal, except for slight eosinophilia (Hodgkin's disease?)."

An examination of bone marrow, a specimen of which was obtained by sternal puncture, showed: polymorphonuclear cells, 50 per cent; metamyelocytes, 4 per cent; premyelocytes, 0; myelocytes, 1 per cent; myeloblasts, 2 per cent; eosinophils, 4 per cent; eosinophilic myeloblasts, 1 per cent; monocytes, 4 per cent; lymphocytes, 34 per cent, and monoblasts, 1 per cent. Comment by the hematologist: "The apparent increase in lymphocytes was probably due to laboratory technic."

Studies of the blood chemistry on Oct. 6, 1943 revealed a fasting glucose level of 80 mg. per hundred cubic centimeters; nonprotein nitrogen, 34 mg.; uric acid, 3.6 mg.; calcium, 10 mg.; albumin, 4.5 mg., and globulin, 3.5 mg.

A roentgenologic study of the chest on Dec. 20, 1943 revealed that "lung fields were overexpanded but otherwise clear. In the right lung, subapically, there was a Ghon lesion ("Ghon" complex—primary infiltration in lung with hilar lymphadenopathy) and calcification at the hilus. The aorta was redundant. No definite mediastinal adenopathy was identified at this examination."

A roentgenologic study of the lateral aspect of the skull on Oct. 22, 1943 showed that "the sella turcica was normal in size and shape. Calcification in the pineal body was at the anterior margin of the average in position."

Histologic studies: Biopsy specimens were taken from the ear and the forehead on three different occasions and were examined by Dr. Nelson Paul Anderson, dermatologic consultant in the department of pathology at the hospital.

The first specimens (figs. 3 and 4), taken on Oct. 4, 1943, were particularly notable for deep cystlike formations arising from greatly dilated follicles and surrounded by moderately heavy cellular infiltration composed mostly of lymphocytes, eosinophils and plasma cells. There were hypertrophy of the epidermis with elongated rete pegs and some dilatation of the capillaries of the upper layer of the cutis.

The second biopsy, on Nov. 5, 1943, was from the ear, and the structure suggested a peculiar type of basal cell epithelioma with cystic degeneration in the isolated groups of cells. This section had been misplaced and was not available for photomicrographing.

The third set of biopsies was made on Jan. 24, 1944 from the ear and the forehead, and the opinion was expressed that the observations were compatible with lymphoblastoma. Only one of the first and third sections was later available for photomicrographing, and it could not be determined whether the tissue was from the forehead or from the ear.

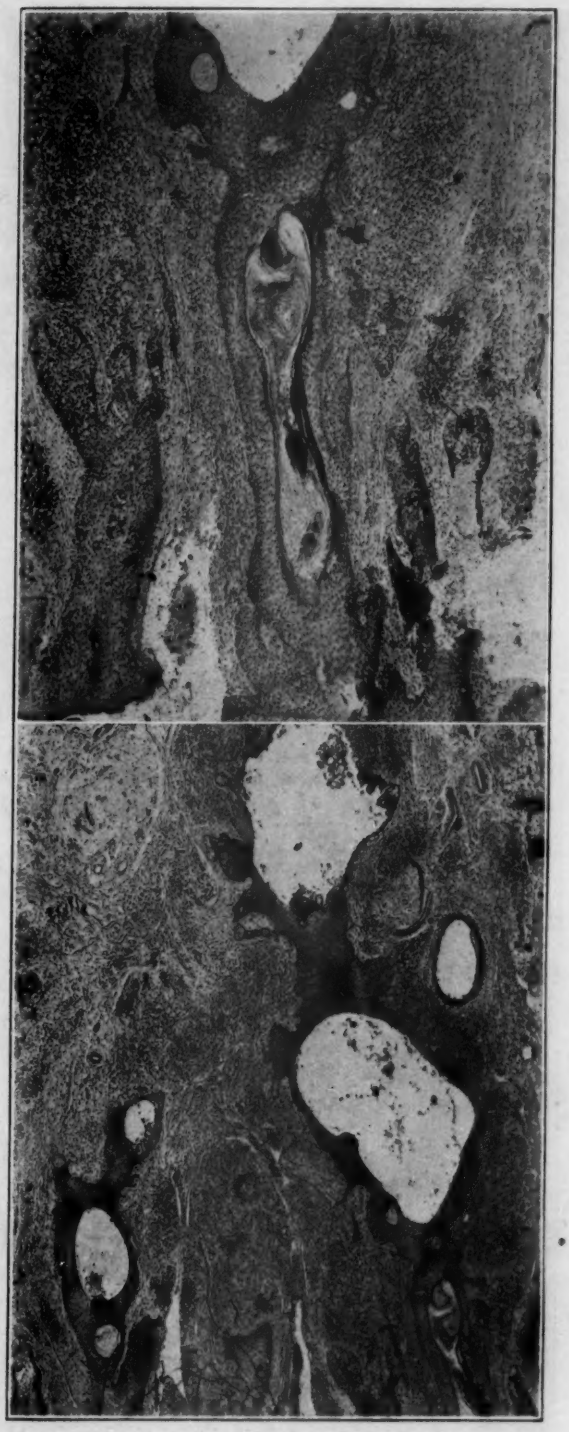

Fig. 3.—Specimens from the ear, showing thickened epidermis and dilated follicles and terminating in cystlike dilatations and cellular infiltration.

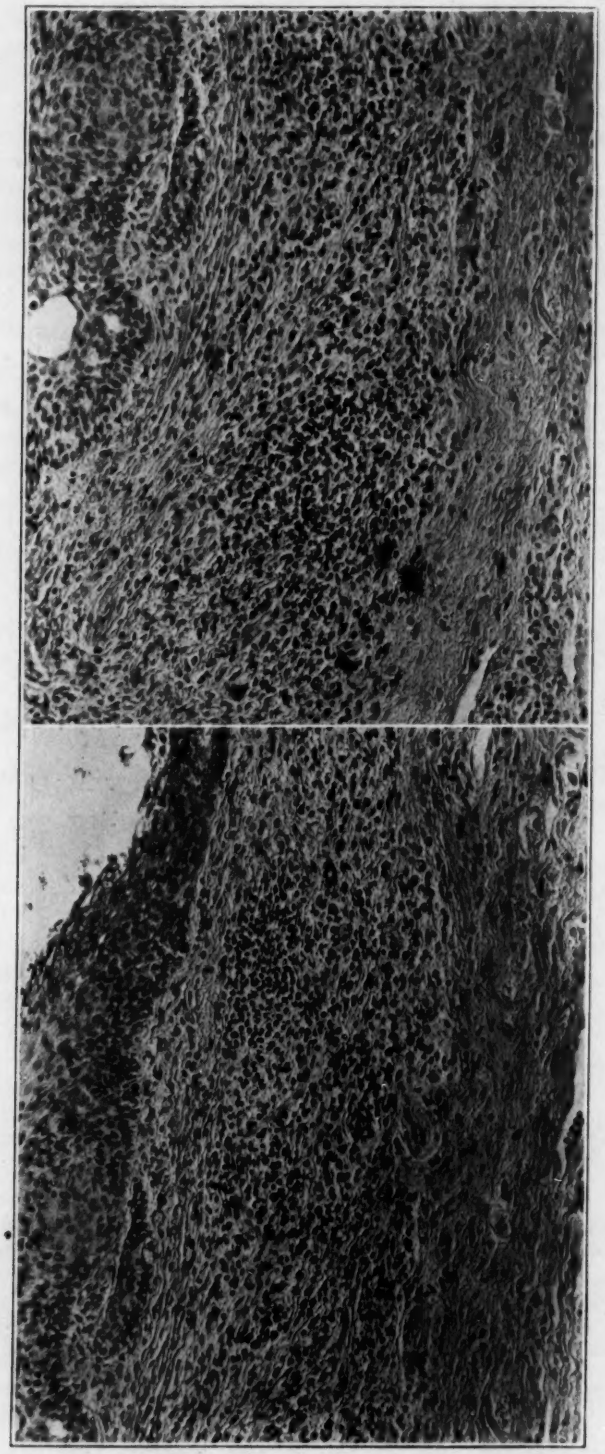

Fig. 4.—High power magnification of tissues seen in figure 3, showing the infiltrate composed of lymphocytes, plasma cells and eosinophils.

In this section (figs. 5, 6 and 7) the epidermis showed little, if any, abnormality. One large epithelial cystlike structure occupied a conspicuous location in the upper layer of the midcutis. A dense infiltrate was present in the upper layer of the cutis and extended to the deeper portions, especially surrounding the cyst. This infiltrate was polymorphous, consisting mostly of small round cells with some plasma cells, some cells of miscellaneous type, a few polymorphonuclear neutrophils and a few eosinophils, but not so many eosinophils as in the first specimen.

Fig. 5.—Section of tissue showing large epithelial cystlike structure and dense lymphoblastoma-like infiltration.

Bacteriologic studies of scrapings and pus from paronychial areas were made on Oct. 28, 1943. A smear showed epithelial cells, a few staphylococci and gram-positive bacilli. A culture for Staphylococcus albus on Sabouraud's medium showed no growth.

(Clinical note: Of the two attending dermatologists who first saw the patient in the dermatologic clinic, one offered a diagnosis of possible mycosis fungoides while the other suggested alternatives of lymphoblastoma or leprosy.)

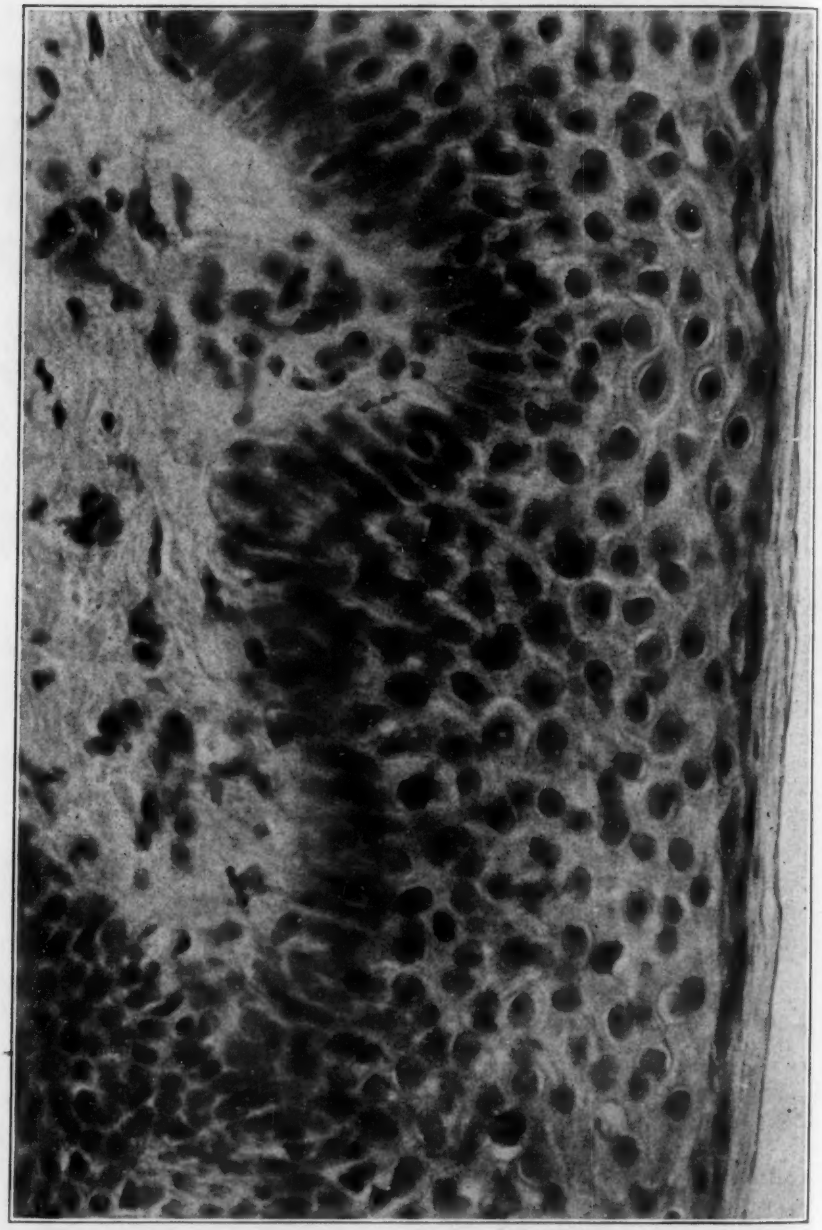

Fig. 6.—Little change in epidermis. Infiltrate seen in the upper layer of cutis.

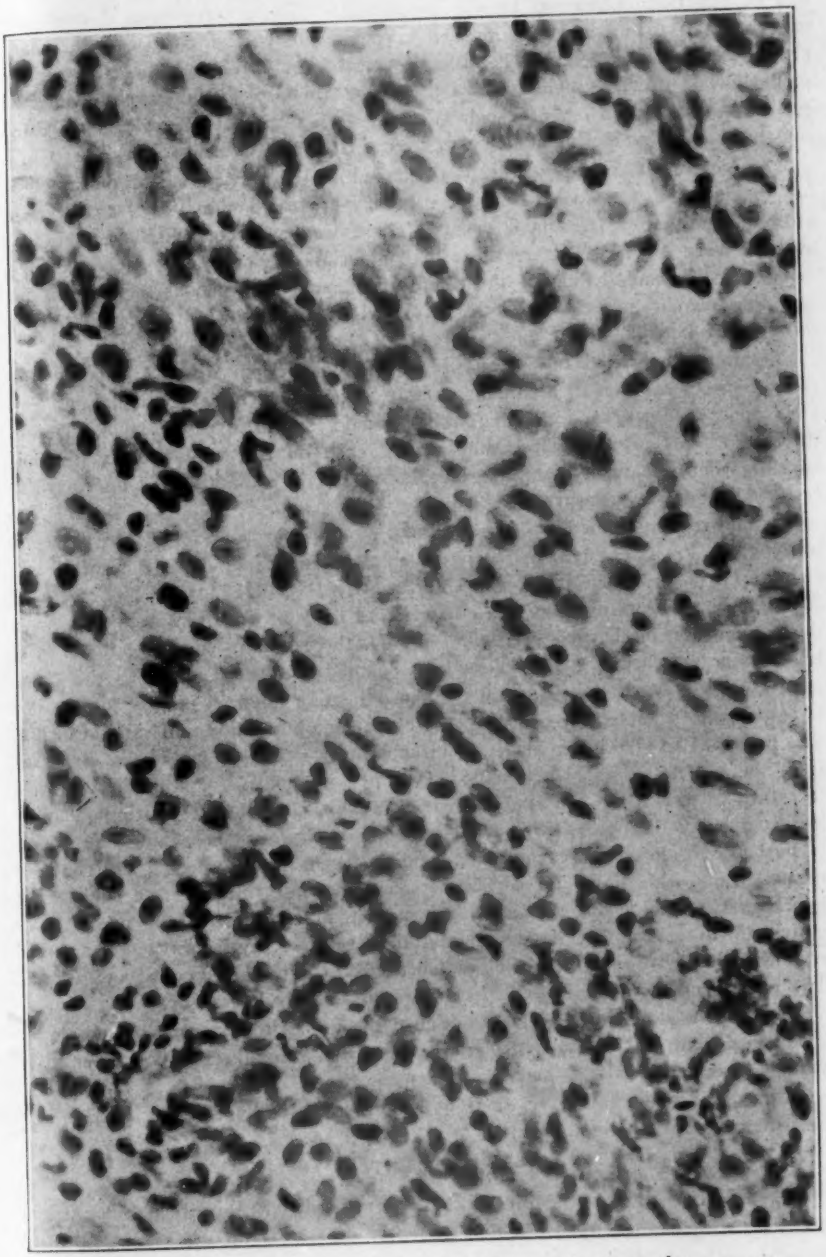

Fig. 7.—Dense polymorphous infiltrate in the cutis.

On Nov. 11, 1943, the patient was referred to the rectal clinic for a search for foci of infection. Comment by the consultant: "There were several cutaneous tags, a small fistula and one infected crypt in the posterior part of the anus. Further search was deferred because of rectal pain. I believe that this patient should have surgical examination of the anus. He also should have the infected crypt and anal fistula operated on. Whether or not the pathologic changes listed constitute sufficient foci of infection to affect his skin is difficult to say."

On Nov. 2, 1943, the patient was referred to the ear, nose and throat clinic for examination for foci of infection, which revealed that the "tonsils were atrophic and had a few small crypts. There was a mucoid discharge, but the airways were otherwise clear. The small anterior cervical glands were palpable. Some crusting and scaling of the canals of the external ear were present. The tympanic membranes were fibrotic. No foci of infection in the ears, nose or throat were noted."

Treatment consisted of various types of topical applications, including wet compresses of solution of aluminum acetate, alibour water (water containing zinc and copper sulfates) and solution of boric acid, several types of shake lotions, three exposures of roentgen rays of 150 r each on the ears, autohemotherapy, various sedatives and a diet high in calories and in vitamins. No improvement resulted from these measures.

Administration of methyl testosterone by mouth in a dose of 10 mg. was begun on Nov. 11, 1943. The patient received a total of thirty-four doses each of 10 mg. except the doses which he received for a period of five days, which were of 20 mg. each. The medication was administered daily or on alternate days. When the patient was discharged, on Feb. 14, 1944, three months after treatment with testosterone was begun, his condition was definitely improved.

The patient was not seen again till approximately nineteen months later, when in response to a letter he reported to the clinic for observation. His appearance at this time was in striking contrast to his appearance at the time of his discharge from the hospital. His condition had continued to improve, so that he was able to return to work. He had experienced no relapse. The itching and inflammation had completely disappeared. The enlargement of the ears, nose and superciliary areas had subsided. There was still some enlargement of the ears, especially of the lobes, and also of the nose. The ears and the nose showed some evidence of hypertrophy of sebaceous glands with formation of comedos. There was a moderate growth of hair on the scalp, and the eyebrows, eyelashes and beard had regrown, although there was little hair on the body. The finger nails were normal. The general appearance of the patient was considerably less senile.

The patient stated that he had continued the use of testosterone by mouth for about one month after leaving the hospital, but that since then, or for a period of about a year and a half, he had taken no medication.

A urologic examination revealed a benign prostatic hypertrophy, which was consistent with the patient's age.

COMMENT

It is, of course, possible that the unusual combination of clinical manifestations encountered in this case were purely coincidental and bore no relationship to one another. This would appear unlikely, however, in view of the fact that all the symptoms began to disappear promptly on the administration of androgenic hormone. It would seem more probable that they were intimately related and constituted a peculiar symptom complex.

Not only was the clinical appearance puzzling, suggestive of a type of lymphoblastoma to a number of competent dermatologists, but the same type of diagnosis (i. e., leukemia and Hodgkin's disease) occurred on at least two occasions to a hematologist as the result of studies of the blood, and again a diagnosis of lymphoblastoma was suggested by the observations in at least one of the histologic sections.

It is conceivable that the generalized pruritic eruption with inflammatory hypertrophy of the face, ears and nose in our patient may represent a bizarre complication of senile pruritus, with the hypertrophy having resulted from an excessive degree of itching and scratching.

Probably the most curious element in the whole picture is the fact that the condition did not recur when the hormone was discontinued. It would almost appear as though the hormone given over a relatively brief period (four months) could initiate physiologic processes which could continue under their own impetus. The situation may be analogous to that of a pendulum of a clock which has run down. Even after the clock has been rewound it is necessary to swing the pendulum by hand in order to start it going again. Perhaps the stimulus of the testosterone in this case was capable of reviving some physiologic mechanism, even though that stimulus was later withdrawn. Such a situation would be contrary to the observations of Dobes, Jones and Franks [3] in the treatment of senile pruritus with testosterone. They observed a tendency of the disease to recur after cessation of treatment. They also failed to secure benefit from the oral administration of testosterone, but obtained favorable results in 7 of 10 patients when the drug was given by injection or inunction.

Hollander and Vogel [4] also reported good results from the daily inunction of 4 mg. of testosterone propionate in a series of 8 cases of what they considered to be senile pruritus and even in several cases of recalcitrant eruptions following known externally irritating factors. There was a tendency to relapse on discontinuance of treatment, although several patients were reported as having remained well. The period of observation, however, was not stated.

Feldman, Pollock and Abarbanel [5] reported a series of 16 patients, both male and female, suffering from senile pruritus, with and without dermatitis. Of the 16 patients good results were obtained in 12,

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3. Dobes, W. L.; Jones, J., and Franks, A. G.: Testosterone Propionate in Treatment of Senile Pruritus, J. Clin. Endocrinol. **5**:412-418 (Dec.) 1945.

4. Hollander, L., and Vogel, H. R.: Testosterone Propionate in Treatment of Male Postclimacteric Dermatoses, Arch. Dermat. & Syph. **45**:356 (Feb.) 1942.

5. Feldman, S.; Pollock, J., and Abarbanel, A. R.: Treatment of Senile Pruritus with Androgens and Estrogens, Arch. Dermat. & Syph. **46**:112-127 (July) 1942.

and the other 4 were considered to have been under treatment an insufficient length of time to have had satisfactory results. The treatment was given by subcutaneous injection with a dose of 10 mg. of testosterone propionate in the men and 1 mg. of estradiol dipropionate in the women at intervals of five to seven days. They did not consider the treatment as resulting in a cure because of a tendency to relapse, but felt that the benefit could be continued by maintenance doses.

Perhaps rhinophyma may be related to a deficiency of male hormone, or more properly, to the rather complicated changes associated with the male climacteric. So far as we know, no one has ever advanced this theory, and we are not acquainted with any observations bearing on this subject, although rosacea, which is a common precursor of rhinophyma, has in some cases in women been ascribed to hormonal changes associated with the menopause. However, rhinophyma occurs predominantly in men and severe rhinophyma occurs almost exclusively in men and usually in men past middle life. The process consists of hypertrophy of the sebaceous glands and follicles. It usually involves the nose and may involve the forehead, chin and cheeks. Involvement of the ears is probably rare.[6]

The clinical picture presented by our patient was obviously not of simple rhinophyma, but there were elements of rhinophyma in it. This was more apparent after the process had subsided. The hypertrophy of sebaceous glands of the nose and of the lobes of the ears is obvious in figure 2. It is conceivable that the peculiar appearance of our patient may have been due to a combination of senile pruritus and rhinophyma.

The lymphoblastoma-like infiltrate possibly represented a severe inflammatory reaction. The dsytrophy of the nails may have been secondary to inflammatory changes of the skin with paronychia or to a primary hormonal effect, or may have been associated with the alopecia totalis.[7]

The subject of alopecia totalis and its relation to the entire picture is most interesting. The cause of alopecia areata and its extreme form, alopecia totalis, has been the subject of much debate, but no one has yet succeeded in establishing a definite causation. This disease may develop at any age and in either sex.

Waisman and Kepler [7] have studied the records of 138 patients with alopecia totalis who were examined at the Mayo Clinic and have drawn the following conclusions: 1. No gross clinical evidence of any

6. Senear, F. E., and Weichselbaum, P. K.: Rosacea and Rhinophyma (Nose and Ear Lobes), Arch. Dermat. & Syph. **52**:201 (Sept.) 1945.

7. Waisman, M., and Kepler, E.: Alopecia Areata: Appraisal of Endocrine Factors in Its Causation, J. A. M. A. **116**:2004-2006 (May 3) 1941.

consistent functional abnormality of the internal secretions could be observed. 2. The instances in which concomitant features of definite endocrine disease occurred were relatively few, and the associations appeared to be incidental rather than causal. 3. The unfavorable prognosis for the regrowth of hair in total alopecia was emphasized by the fact that only 4 of the 138 patients completely recovered. 4. Endocrine treatment up to the time of the report (1941) was ineffectual. 5. No other accompanying cutaneous disturbance in any of the cases was mentioned, except disturbances in growth and structure of the nails (pitting, longitudinal furrowing and thickening or thinning of the plates), which was frequently observed. There were also 9 cases of vitiligo and 3 cases of chloasma. 6. The age of onset ranged from 4 years to 69 years, with the greatest frequency in the decade between 20 and 30.

In the case of our patient it would be difficult to discount the influence of the testosterone in bringing about a regrowth of hair in view of the facts that the alopecia had been of fifteen years' duration and no other treatment, either local or systemic, had been used since the administration of testosterone was begun.

One might argue that the administration of testosterone should have an adverse effect on growth of hair in view of the common occurrence of baldness among men. Alopecia in men, however, is merely a pattern of distribution of hair determined by a combination of hereditary predisposition and the effect of the male hormone. In normal baldness in men, even in extreme cases, usually a fringe of hair about the sides and back of the scalp is left and the lashes, brows, beard and body hair are never affected. Hamilton [8] demonstrated conclusively the relationship between the male hormone and so-called premature alopecia in observations on a series of 54 sexually immature men who either were eunuchoid or had been castrated prepubertally or during adolescence. None of them presented this premature alopecia, in contrast with an incidence of about 43 per cent in normal adult men. After the administration of testosterone the typical male pattern of alopecia developed in the men whose family history showed a strong tendency to baldness.

There is no contradiction, therefore, in the apparent capacity of testosterone to stimulate growth of hair in the patient herein reported. It would be fallacious, however, to draw the conclusion that all cases of alopecia totalis are caused by deficiency in hormones or that a cure would result with hormone therapy. Normal pregnancies were recorded by Waisman and Kepler in several women with alopecia totalis, indicating no deficiency of sex hormones.

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8. Hamilton, J. B.: Male Hormone Stimulation Is Prerequisite and an Incitant in Common Baldness, Am. J. Anat. **71**:451-480 (Nov.) 1942.

Rony and Zakon [9] reported the clinical and histologic effects of administration of androgen and estrogen in 2 apparently normal men. One man, who was 18 years old, presented an early but moderately extensive premature alopecia, and the other, who was 34, had subtotal alopecia areata. Methyl testosterone administered by mouth produced a definite stimulation and hypertrophy of sebaceous glands of the scalp in both men. A slight growth of lanugo hair with itching appeared in the bald areas of the scalp of the man with alopecia areata, who in addition to receiving 40 mg. of methyl testosterone by mouth daily for four months received 25 mg. of testosterone propionate twice a week by injection. The total effect of stimulation however was regarded as negligible. After a period of rest, however, and subsequent administration of 5 mg. of diethylstilbestrol daily for one month there was such a loss of scalp hair and other hair that the patient refused to take any more estrogen. The patient with premature alopecia received 5 mg. of diethylstilbestrol for three months without noticeable effects on the scalp hair, although there were definitely stimulating effects on the breasts. In both patients, biopsies revealed depressing effects with some atrophy of the sebaceous glands of the scalp.

Finally, a study of the photographs of our patient taken after he had recovered, or about nineteen months after he had left the hospital, gives the impression of a man five to ten years younger than he appears in the photographs taken during the height of his disability. The difference in appearance may, of course, be due in part to the growth of hair and the relief from intolerable itching.

SUMMARY

An unusual clinical picture is presented consisting of the case of a 66 year old man who had been totally bald for fifteen years and who later experienced a generalized pruritic eruption associated with inflammatory hypertrophy of the nose, ears, chin, cheeks and superciliary areas and decided dystrophy of the nails. Histologic examination of a specimen of tissue removed from the ear revealed a lymphoblastoma-like infiltrate in the cutis and decided dilatation of the follicles with cystlike formation. The entire clinical picture cleared up after four months of treatment with testosterone administered by mouth. When the patient was seen, nineteen months after his discharge from the hospital, the improvement had been maintained without further treatment, and there was a residual moderate hypertrophy of the sebaceous glands of the nose and ear lobes suggestive of rhinophyma of mild degree.

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9. Rony, H. R., and Zakon, S. J.: Effect of Endocrine Substances on the Adult Human Scalp, Arch. Dermat. & Syph. **52**:323-327 (Nov.-Dec.) 1945.

ABSTRACT OF DISCUSSION

DR. MARCUS R. CARO, Chicago: Dr. Ayres is to be congratulated on the response to treatment that he obtained in this strange case. The improvement is more gratifying because of the advanced age of the patient and the long duration of his alopecia, since both factors generally have an adverse effect on the results.

A positive finding is always more significant than a negative one. Waisman and Kepler reported in 1941 on a study of 138 cases of alopecia areata in which they observed no abnormality of function of the endocrine glands. If one may assume in the case being presented today that the response to treatment with methyl testosterone indicates a causative endocrine disturbance, the case takes on considerable importance.

In spite of the simultaneous improvement in the alopecia and the cutaneous lesions, I cannot be certain that they all are part of one symptom complex. I have never seen a case that parallels this one, but on examination of the photographs it is suggested to me, as it was to Dr. Ayres and Dr. Jensen, that there may have been a combination of senile pruritus, rosacea and possibly seborrheic dermatitis, with changes in the nails secondary to scratching and infection.

The histologic sections showed cystlike structures with a polymorphous infiltrate about them, such as are often seen in rhinophyma. The presence of such a wide variety of cells in the infiltrate speaks strongly against a diagnosis of lymphoblastoma.

I am grateful to Dr. Ayres for this presentation and for calling my attention to methyl testosterone in the treatment in hitherto discouraging cases of alopecia totalis.

DR. GEORGE C. ANDREWS, New York: I am rather sure that testosterone is of no use in the treatment for alopecia totalis in women. I have treated 2 patients thoroughly and carefully with it without noting any improvement.

DR. SAMUEL AYRES JR., Los Angeles: I want to thank the discussers. I presented this case with a good deal of hesitation because I know that one is always assuming some risk when one presumes to present what appears to be an unusual clinical entity, and I am not certain that this is more than a coincidental combination of symptoms. Yet the striking response of all of the patient's symptoms to the one therapeutic agent, together with the encouraging communication I received from Dr. Tobias, in which he stated that he had an identical type of case, led me to present it. I questioned Dr. Tobias in detail, and apparently his case coincided in every respect with mine, including the favorable response to treatment. It may be that there is some peculiar manifestation of the male climacteric which can produce a picture of this sort.

It was particularly striking, again, in view of the reaction of practically every one who saw this patient. Hardly any of the dermatologic staff questioned the likelihood that this was a case of some peculiar form of lymphoblastoma, and that again makes it more interesting in view of the therapeutic response.

Obituaries

ARTHUR WHITFIELD, M.D.

1868-1947

By the death of Arthur Whitfield on Jan. 31, 1947, at the age of 79, dermatology has lost not only one of its outstanding figures but also a most attractive personality.

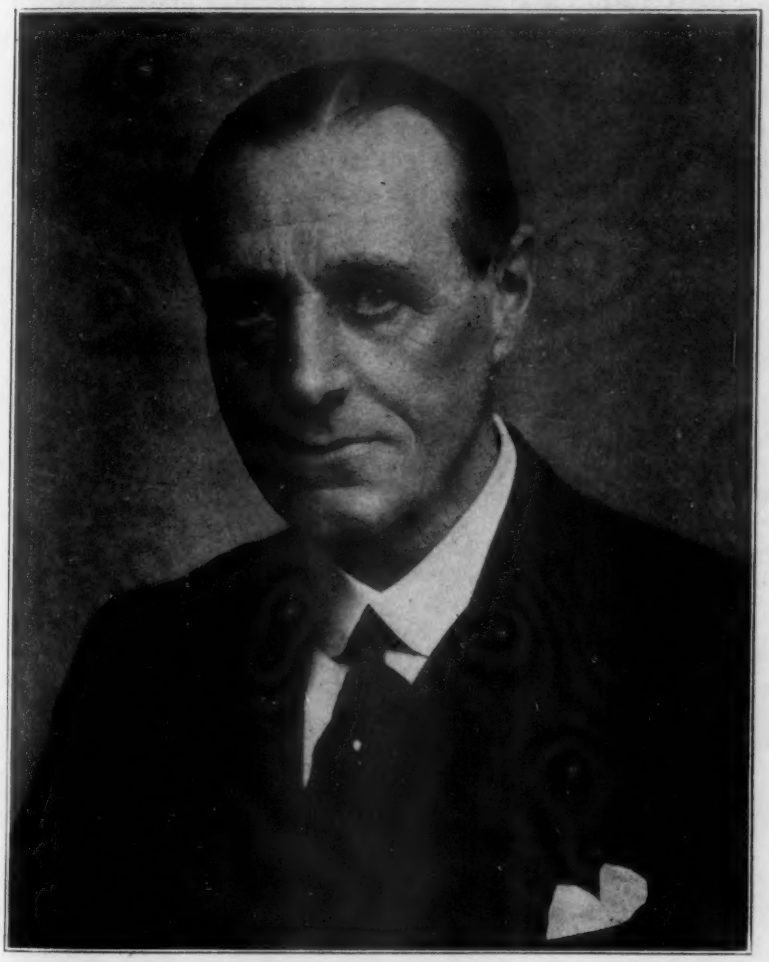
He studied medicine at King's College Hospital, London, and, after holding a number of junior appointments there, he spent three years, from 1893 to 1896, in Vienna and Berlin, attending the clinics of Kaposi and Neumann among others. On his return to England he was appointed dermatologist to the Royal Northern Hospital and later physician to the Skin Department at King's College Hospital, becoming Professor of Dermatology in King's College in 1906, which post he held until his retirement in 1927.

Among the leaders in dermatology in England at this time were Jonathan Hutchinson, Radcliffe-Crocker, Colcott Fox, Malcolm Morris, Pringle and Brooke, and as a member of the London Dermatological Society, then an exclusive society, he was able to study their methods and join them in their discussions. Of these men Colcott Fox influenced him most, and he for some time assisted him at Westminster Hospital. From Colcott Fox he learned to study cases with that care for detail which characterized his work during his whole career.

Entering the field of dermatology when knowledge of bacteriology and mycology of the skin was in its infancy, Whitfield threw himself with vigor into a study of these subjects. He published papers on the bacteriology of acne vulgaris and later, stimulated by the work of Almroth Wright, made a careful study of vaccine therapy in cutaneous diseases, opening a discussion on this subject at the International Congress of Medicine in 1913. He is best known, however, for his discovery of the causative role of fungi in tinea pedis. His observations, published in the *Lancet* in 1908, preceded by two years similar observations made by Sabouraud. This discovery was not a casual one, but the result of systematic microscopic examination of scales, which he always carried out. Later he introduced the ointment known by his name for the treatment of this disease, which, in spite of exhaustive investigations into new fungicides, still holds a valuable place in the treatment of fungous diseases.

The histology of the skin also intrigued him. He published papers on nevocarcinoma and osteitis deformans and, in conjunction with G. A. Harrison, a study of xanthomatosis. His work on erythema

induratum in middle-aged persons, published in 1909, opened fresh ground in the study of hypodermic nodules of the lower limbs. Later he turned his attention to the study of autolytic processes underlying the production of eczematous lesions, which he elaborated in his Lumleian Lectures at the Royal College of Physicians in 1921 and at the International Congress of Dermatology in Copenhagen, Denmark,



ARTHUR WHITFIELD, M.D.
1868 - 1947

in 1930. He also wrote on many other subjects, which are too numerous to mention here.

He held many offices in the dermatologic societies in his own country and was a member of a number of foreign societies. He was proud of his corresponding membership in the American Dermatological

Association, Inc., and always remembered with pleasure the meeting of the International Congress held in New York in 1907, which he attended.

Whitfield had a vivid and attractive personality. He seemed to possess perpetual youth. Even in his later years, when he was somewhat cripplied by painful rheumatic spondylitis, this characteristic never left him. He had the curiosity of a boy and was never satisfied till he had found out all that there was to know about any problem which he attacked. At meetings he often threw fresh light on old problems and never hesitated to express his views in a vigorous manner. There can be no doubt that the influence which he exercised on his colleagues, especially his juniors, was far reaching and that by his death dermatology is poorer for the loss of an outstanding personality.

Society Transactions

LOS ANGELES DERMATOLOGICAL SOCIETY

Clement E. Counter, M.D., *Chairman*
Maximilian E. Obermayer, M.D., *Secretary*

Nov. 13, 1945

Adenoma Sebaceum, Pringle Type. Presented by DR. H. C. L. LINDSAY.

Erythema Induratum and Sarcoidosis (with Erythema-Annulare-Like Lesions). Presented by DR. MOLLEURUS COUPERUS.

B. M., a white woman aged 59, born in the United States, had been in fairly good health until three years ago when a gangrenous appendix was removed. At the time it was noted that the spleen was palpable 2 fingerbreadths below the costal margin. While the patient was in the hospital there developed abscesses in the eye, which resulted in glaucoma and subsequent loss of sight in both eyes. On both legs scaling plaques developed, which after many months disappeared, leaving no trace. Four months ago the present eruption developed, accompanied with a mild burning sensation.

On the back and front of both legs there are annular and oval lesions, some 10 cm. long and 5 cm. wide, consisting of a fine erythematous, 3 to 4 mm. wide, barely palpable, slightly elevated border and a more or less normal-appearing center, suggesting erythema annulare centrifugum. The lesions are not tender, and no loss of sensation is discernible.

The eyeballs protrude from their sockets, are irregular in contour and seem to contain many cysts and perhaps small abscesses. Both eyes are insensitive to light. The spleen is firm and enlarged to below the level of the umbilicus.

The Wassermann and Kahn reactions were negative. The leukocyte count was 2,800 with 17 per cent lymphocytes on one occasion and 1,500 on another. Roentgenograms revealed that the chest and the long bones of the hands were normal.

Histologic examination of one of the lesions performed in December 1943 showed the features of sarcoid of Boeck. Examination of a specimen recently removed from the border of one of the present plaques disclosed that the epidermis was somewhat irregular and acanthotic in one area but otherwise essentially normal. The upper part of the dermis showed a mild lymphocytic perivascular infiltrate. Between the fat cells of the hypoderm was a heavy infiltrate of epithelioid cells and lymphocytes. This infiltrate extended in two areas up to the sweat glands. Just above the hypoderm there was some tubercle formation, but only two or three giant cells were present in the sections.

DISCUSSION

DR. L. H. WINER (by invitation): Clinically I could see no features in favor of a diagnosis of erythema induratum. The lesion resembled sarcoid. The histologic picture was interesting in that the epidermis and connective tissue were not involved, but the subcutaneous fat was implicated in a process in which the fat was being replaced by infiltration. Apparently these are old lesions and could represent the final stage of old erythema induratum, considering that erythema induratum is a tuberculous thrombophlebitis in the subcutaneous fat and that replacement

of this subcutaneous fat by infiltration of lymphocytes and organization of the thrombus appears plausible.

DR. MOLLEURUS COUPERUS: I do not believe that these lesions at any time were different from what they are today, except perhaps that they are a little lighter than they were four weeks ago. When I first saw the patient I thought that this was probably a transient eruption. The past history of the patient and the rather solid feeling of the margins of the lesions caused me to perform a biopsy. I believe that this patient does have sarcoidosis and more recent erythema induratum, an assumption which I think is supported by the microscopic sections from the two different lesions. The intense splenomegaly is not easily explained except by the assumption of sarcoidosis. Involvement of the eyes may also occur in this disease. The only question that one might have is whether the lesions on the legs are true Bazin disease or a deep form of sarcoid. The histologic picture does not seem to indicate the latter. From my perusal of the literature, it must be rare to see both sarcoidosis and erythema induratum simultaneously in a patient, but I believe that this is the case. The additional unusual feature is the erythema-annulare-like clinical appearance of the plaques, which are histologically erythema induratum.

A Case for Diagnosis (Mycosis Fungoides?). Presented by DR. SAMUEL AYRES JR.

Sarcoid of Boeck. Presented by DR. HARVEY STARR (by invitation) and DR. MOLLEURUS COUPERUS.

A Case for Diagnosis (Lepra? Dermatitis Factitia?). Presented by DR. A. FLETCHER HALL.

A white man aged 23, of American stock, who as a soldier had served in the North African and Italian campaigns, awoke one morning in March 1945 in Italy to find a red lesion on the right side of his forehead. The lesion did not subside, but gradually became scaly and has persisted practically unchanged for the past six months. Three months after the lesion was noticed a depigmented spot appeared on the front of the upper part of the right thigh. The new lesion, which was asymptomatic, gradually became enlarged, with loss of hair in the involved area. Later, central pinkness and scaling appeared. Since then numerous patches of a similar nature have appeared on the thighs and arms. The lesions progressed only to a certain point. There has been no itching.

The right side of the forehead is the site of an irregular, round, half-dollar-sized, mildly infiltrated, slightly pink and scaly plaque. The front and sides of both thighs show numerous irregularly scattered and depigmented round and oval patches in various stages of evolution. The youngest lesions are pea-sized depigmented patches, with irregular ill defined borders. The oldest lesions are larger and depigmented, with more regular well defined borders and loss of hair, while the oldest patches are similar but show in addition central erythema and scaling. The older lesions appear slightly infiltrated. A few lesions which appear bald show a few palpable tiny hair stubs near the center. The lesions are hyperesthetic to pinpoint stimulation.

The Wassermann and Kahn reactions of the blood were negative. No acid-fast bacilli were observed in curetted nasal material. No fungi were observed in microscopic examination of scales. Culture of scales on Sabouraud's medium yielded no growth. The blood count was normal.

Histologic examination of the lesion in the forehead showed that the stratum corneum was decreased in thickness and displaced from its normal attachment during fixation. No parakeratosis was seen. The stratum granulosum was thin

throughout and absent in some areas. The prickle cell layer was of normal thickness in some areas, while in others the tips of the papillae approached the granular cell layer closely. There were hair follicles rather closely set, and follicular plugging was seen in some of them. The dermis was the seat of diffuse round cell infiltration with some perivascular and perifollicular localization, but it was located to the greatest extent around the sweat glands. There was decided dilatation of blood vessels extending deep into the dermis. The connective tissue elements were normal. Some smooth muscle of normal appearance was seen.

While the patient was in the Army the disease was treated with various fungicidal preparations, but no improvement was obtained.

DISCUSSION

DR. HAL E. FREEMAN: Pityriasis versicolor leprosy, ordinary vitiligo, leukoderma and achromia parasitica have been ruled out. The possibility of dermatitis factitia cannot be excluded. The inflammation which is present appears to be secondary. The hypopigmented areas develop first and the inflammation later, a fact which makes me think that the lesions may be self imposed.

DR. Anker K. JENSEN: I would suggest that lepromin and histamine tests be performed.

DR. M. E. OBERMAYER: I have no diagnosis to offer, but I should like to point out the valuelessness of using nasal scrapings in investigating lepra. While involvement of the nasal mucosa is fairly common in lepromatous lepra and mycobacteria can be demonstrated with ease in nasal scrapings in such cases, it is not uncommon to find acid-fast diphtheroid bacilli morphologically indistinguishable from Mycobacterium leprae in the nasal mucous membrane of healthy persons and lepers. Consequently, the presence of acid-fast bacilli does not mean that the subject has lepra nor does their absence indicate freedom from the disease.

DR. NELSON PAUL ANDERSON: I have seen 1 or 2 similar cases. A search for fungi and other causative agents is fruitless. I believe that this disease is some form of bacterial infection, probably of a low grade type. There is something about it that does not fit in with a fungous infection.

DR. SAMUEL AYRES JR.: There was something about the lesions on the forehead which appeared different from those in other areas. I would not be surprised if the eruption would eventually prove to be lymphoblastoma.

DR. A. F. HALL: I think that Dr. Freeman's suggestion of dermatitis factitia must be kept in mind. That is the only diagnosis that I can conceive of consistent with the history of these lesions and their appearance. I am not familiar with any fungous infection which would cause a primary depigmentation followed by squamous manifestations rather than in the reverse order. I can conceive of the application of a bleach, such as solution of mercury bichloride, to an area with resultant depigmentation and further applications of the same chemical resulting in an inflammatory reaction followed by scaling. This patient has a rather apprehensive mien, and there is something strange in his attitude toward his dermatosis that I am not able to define or interpret. The flare reaction to histamine was normal. Pinta might be possible, except that the negative reactions in the blood tests militate against it. There has been no dark field examination of scrapings.

Hemangiomas of the Scrotum (Angiokeratoma of Fordyce?). Presented by DR. SAUL S. ROBINSON and DR. SAMUEL TASKER (by invitation).

R. N., a white man aged 61, noticed the development five years ago of lesions on the scrotum, which slowly increased to the present size. There are no symptoms.

The patient suffered from gastric ulcers and arthritis but has not had a hernia, surgical treatment of the abdomen or varicocele.

On the scrotum, especially on the right side, are multiple, discrete, bluish red, elevated, matchhead-sized nodules. Capillaries are present on the scrotal skin.

The Wassermann and Kahn reactions of the blood were negative, and the urine was normal.

DISCUSSION

DR. L. F. X. WILHELM: I think that this case is a typical example of angiokeratoma of Fordyce.

DR. L. H. WINER (by invitation): In angiokeratoma there must be hyperkeratosis. Angiokeratoma occurs on the lower extremities after frostbite or trauma. Histologically, angiokeratoma is typical in that there is a large blood space covered by epidermis with a thick layer of stratum corneum on top. These lesions on the scrotum of the patient presented are more in the nature of angiomas. Keratoma is not part of it. It may be called an angioma of nevoid type, but not an angiokeratoma.

DR. SAMUEL TASKER (by invitation): Several months ago my colleagues and I had a patient with similar lesions. From histologic examination we concluded that "angiokeratoma" was a misnomer and that the lesions really were angiomas.

DR. SAUL ROBINSON: These cases are of interest since Fordyce first described a case of angiokeratoma about fifty years ago. A history of surgical treatment of the abdomen, hernia or varicocele with circulatory impairment is usual, and the patient is usually middle aged or senile. The angiokeratoma of Mibelli is observed in younger persons, with chilblain, or pernio. The lesions in angiokeratoma of Mibelli are keratotic, superimposed on angiomas and often seen on the dorsum of the fingers and toes.

Varicelliform Eruption of Kaposi. Presented by DR. A. FLETCHER HALL.

J. C., a white boy aged 15, had had eczema and asthma since he was 8 months of age. The eczema has been limited to the neck, cubital fossae and popliteal spaces, but more recently the hands and the lower part of the face have become involved. He had had herpes simplex in the past. Vaccination against smallpox was performed thirteen years ago.

He had been relatively free from cutaneous trouble all summer and until a week ago, about November 6, when the usual fall exacerbation began. On November 9 he suffered a chill and elevation of temperature in the evening. The next day his temperature rose to 103 F. and he noticed vesicles and pustules appearing in and around the preexisting eczematous patch in the left cubital fossa. Two days later the eruption became generalized and another chill and elevation of temperature occurred in the afternoon. On November 12 the eruption was at its height and another chill and elevation of temperature occurred. It was then that treatment with penicillin was begun in doses of 20,000 units intramuscularly every three hours. Since penicillin therapy was begun no new lesions have appeared, the fever has subsided and the patient feels much better.

The sides of the face and neck, the cubital fossae and the popliteal spaces show rather typical involvement with atopic dermatitis. There are a few similar plaques on the dorsa of the wrists and fingers. Superimposed on these patches and generally scattered over the entire surface of the body are numerous erythematous papules and ruptured vesicles or pustules, with dark crusts suggesting hemorrhage or even necrosis. The crusted lesions are more numerous on the face, neck, shoulders and arms. A few isolated intact varicelliform vesicles and pustules can

be seen on the arms. There is a small group of pustules far back on the left buccal mucous membrane. There is a mild generalized swelling of the lymph nodes and the postcervical region. His temperature (oral) was 99.2 F. at noon. The differential blood cell count was essentially normal.

DISCUSSION

DR. NELSON PAUL ANDERSON: I hesitate to open the discussion in the presence of Dr. Goeckerman and Dr. Wilhelm, who were the first in this country to report the varicelliform eruption of Kaposi. I would accept that diagnosis in this case with a good deal of reservation. The lesions of Kaposi's varicelliform eruption while not particularly limited to the areas of atopic dermatitis are worse in those areas. I have known persons with this disease to be decidedly sick, although my observations were made before the introduction of treatment with penicillin. However, a few patients have been given sulfonamide drugs, which apparently had little if any effect. Not having seen this patient when the disease was severest, I can suggest only that this patient may have had chickenpox, even though chickenpox is uncommon in adults who live in a large city. You are all aware of the work that has been done to establish the herpes virus as the cause of this eruption. The boy gives a history of recurrent aphthous stomatitis for a number of years.

DR. W. H. GOECKERMAN: I agree with Dr. Anderson that this is not Kaposi's eruption. The lesions are manifestly discrete except for the atopic dermatitis, which necessarily would eliminate the diagnosis. Whether vaccinia, chickenpox or some other infectious disease was superimposed on the atopic dermatitis is now somewhat indefinite. The history would suggest that it was. I have been intrigued by the fact that when we reported our first case nine or ten years ago I was unable to find a single report of this disease in the American literature. Now suddenly there are reports from two sources of a number of cases of this eruption seen at the same time. It is possible that such cases are seen by general clinicians or pediatricians without being recognized. However, they present a distinct clinical picture. In recent years almost any eruption the cause of which cannot be explained otherwise is said to be due to a virus. I am still skeptical about this. The intriguing question to me is whether virus of various types is becoming more virulent than it was in years past.

DR. SAUL ROBINSON: I believe that this patient is suffering from pityriasis varioliformis acuta. The onset with fever and constitutional symptoms together with papular, vesicular, necrotic and hemorrhagic lesions has been reported to occur in the cases of acute disease.

DR. SAMUEL AYRES JR.: I have seen 2 cases, both in small children, but the eruption was almost confluent over the areas of atopic eczema. This patient presents no such picture. Instead the lesions are sparsely distributed. If he did not have eczema I should say that he had chickenpox. The patient, however, says that he has had chickenpox in the past.

DR. J. R. SCHOLTZ: I have read Dr. Goeckerman's paper and others, and I am not certain of the criteria on which this diagnosis is established. In the Army, among men vaccinated against smallpox routinely, we saw a number of men with chronic neurodermatitis who soon experienced generalized vesicular and pustular eruptions, more severe on the areas of chronic dermatitis and accompanied with a high temperature. It would seem that the clinical picture and the course of the disease might be determined by the type of virus that causes the infection. For

example, the person who acquires smallpox virus might be more severely ill than the one who acquires chickenpox virus or herpes virus.

DR. C. RUSSELL ANDERSON: I think that it has been well established that Kaposi's varicelliform eruption is due to the herpes virus. These patients have no immunity to the herpes virus, and that accounts for its appearance in children more often than in adults. I have observed 2 adults, both with atopic dermatitis, and both had Kaposi's varicelliform eruption. Neither of them had had herpes previously, but since their attack of the varicelliform eruption they have suffered attacks of herpes simplex. Immunity has not been established in them, and that is the reason for their widespread eruptions. I think that you will learn that persons with Kaposi's varicelliform eruption have never had herpes simplex. I think that in the past many of these cases have been classified as vesiculopustular erythema multiforme. Sutton's book has such an illustration by Sweitzer.

DR. A. F. HALL: I presented this case with the present diagnosis with misgiving, the reason being that there were a few points which did not conform to the diagnosis. However, several points have been brought out in the discussion which I want to clear up. The patient was decidedly ill prior to presentation, but he had been treated with penicillin. Perhaps this case should have been presented as one of dermotropic virus infection superimposed on an atopic dermatitis. He has had repeated attacks of aphthous stomatitis, which I believe is due to the herpes simplex virus. If this disease were to become disseminated, I believe that the eruption would have developed before now. I think that there are other viruses which may cause a similar eruption. If his mother, who is a registered nurse, were not so certain that the patient had had varicella at the age of 3 years, I would be inclined to suspect that disease superimposed on atopic dermatitis. At present this eruption certainly is more disseminated than that in the cases of Kaposi's varicelliform eruption described by Dr. Goeckerman and others. Dr. Goeckerman mentioned seeing such cases in persons in certain localities. In the past year in Santa Monica, Calif., I have seen 2 cases, both in infants under 2 years of age, and both have been cases of typical appearance and history, almost limited to the areas of preexisting atopic dermatitis.

NOTE.—On the fourteenth day after the onset of this patient's eruption, his brother experienced typical severe varicella. His mother still maintains that both the patient and his brother had previously had varicella in childhood.

A Case for Diagnosis (Lymphedema?). Presented by DR. ANKER JENSEN.

A. L., a white man aged 50, was presented on March 9, 1943 (*Arch. Dermat. & Syph.* **48**:475 [Oct] 1943. Since then the lesion has become enlarged. No treatment has been given. The mass extends slightly into both nostrils, including most of the upper lip to a width of about 5 cm. The consistency is doughy.

DISCUSSION

DR. M. E. OBERMAYER: I think that the tumor mass has become enlarged since this patient was presented for the first time and looks today more like typical elephantiasis than it did then. Moreover, the possibility of an angiomatous tumor has now been ruled out by biopsy.

DR. J. WALTER WILSON (by invitation): This localized lymphadenopathy around the face and nose, I was interested to learn, had another name, "Erysipeloid of Fox." It is, as I believe Dr. Obermayer commented two years ago, a bacterial plugging of lymph channels from areas in the face, around the nose mostly. In most of these cases the disease recurs several times before lasting changes are produced. In this patient apparently the feature of recurrence is not present.

DR. J. R. SCHOLTZ: Clinically the lesion feels and looks like chronic granulation tissue. I am not familiar with staphylococcic infection which continues for three years without change and without moving to a new location. I also do not believe that the anatomic situation would permit the development of a lesion like this on the basis of a lymphatic blockage.

DR. HAL E. FREEMAN: I would like to have the presenter rule out granulosis rubra nasi.

DR. W. H. GOECKERMAN: I should like to see this case presented again at some future date. There is no doubt that the whole behavior of the disease is atypical if it should prove to be a so-called solid edema.

DR. WILLIAM MULVIHILL: I suggest the diagnosis of lupus vulgaris tumidus. The microscopic picture is not typical, but there are sufficient features to suggest that diagnosis. The section might be from an area that did not show the typical granulomas of lupus vulgaris. The infiltration with epithelioid cells is enough basis for consideration of one of the true granulomas.

DR. L. H. WINER(by invitation): I agree with Dr. Obermayer's diagnosis of elephantiasis nostras and not lupus vulgaris tumidus. Lupus vulgaris is a disease that begins in early childhood and not as a rule in a mature man. There are no lupus nodules here. Clinically this tumor suggested a hemangioma or lymphangioma, but histologically there were only a few small capillaries in an extensive fibrotic process, which could be the result of an old chronic inflammation. These fibroses are not as hard as those of a keloidal scar.

Balanitis Xerotica Obliterans. Presented by MAJOR RICHARD L. SAUNDERS, Medical Corps, United States Army, Birmingham General Hospital (by invitation).

A soldier aged 27 noticed in July 1942 a painful and tender swelling of the glans penis. Since then the inflammation has been progressive, with alternating remissions and exacerbations. Sexual intercourse has been impossible for the last two months because of the pain. Various local applications have been of no benefit.

On the right side of the glans penis and the corresponding area of the inner layer of the prepuce there is an indurated plaque of firm consistency, purplish borders and an eroded surface.

Histologic examination of the lesion showed an atrophic epithelium with intracellular edema and liquefactive degeneration of the basal layer. Immediately under the epidermis was a thick band of hyaline cellular tissue. Intermingled in the deeper parts of the dermis were foci of infiltration of lymphocytes, plasma cells, a few polymorphonuclear leukocytes and monocytes and many small blood vessels.

DISCUSSION

DR. SAMUEL AYRES JR.: Lesions of this sort on the penis present a difficult problem in diagnosis. In this case the history was of the foreskin's being rather adherent and not easily retracted until a comparatively short time ago. Apparently a chronic irritative process had been present for several years, resulting in the present atrophic and hyperplastic changes. There is an appearance suggestive of leukoplakia. At the same time some thickening suggests the possibility of early malignant change. I am in doubt as to whether the disease should be definitely classed as balanitis xerotica obliterans. The few cases I have seen have usually started around the meatus and have resembled lichen sclerosus et atrophicus. I am not convinced that this is a true case of balanitis xerotica obliterans. I would suggest the possibility of leukoplakia with early malignant change. I think complete excision is the treatment of choice.

DR. L. H. WINER (by invitation): I agree with the diagnosis because the histologic picture is definitely that of balanitis xerotica obliterans. There is atrophy of the epidermis and homogenization of the upper layer of the cutis, with a band of lymphatic infiltration beneath the homogenized zone.

MAJOR R. L. SANDERS (by invitation): I felt that the clinical course was characteristic. It is a chronic slow process. The histologic picture fitted in fairly well with the picture of the case reported by Laymon. I was interested to learn the relationship between this disease and lichen sclerosus et atrophicus.

A Case for Diagnosis: Lichen Ruber Moniliformis (?), Dermatitis Actinica from Roentgen Ray Therapy of Legs. Presented by DR. MAXIMILIAN E. OBERMAYER.

E. P., a white woman aged 45, of American stock, at the age of 12 had mosquito "bites" all over the body while on a camping trip in the mountains of Pennsylvania. The "bites" subsided with the exception of those on the legs, which she scratched, thus preventing their healing and causing the formation of "open sores," which were thought to be from "dye poisoning" from the stockings. The "sores" persisted and were left untreated until the age of 16, when a physician in Philadelphia administered an injection of arsphenamine ("606") and continued what was evidently antisyphilitic therapy for one and one-half years. The "sores" healed rapidly, but a pruritic eruption remained and has persisted until the present time. A course of roentgen ray therapy was given in 1933. In the years which followed the skin over the irradiated area became thinned, and from 1936 on she has been suffering off and on from multiple ulcerations.

The patient was said to have been presented before a dermatologic society at Syracuse, N. Y., about fifteen years ago.

The skin from just above the knees down to the ankles is covered with flat, slightly erythematous or waxy, densely set papules of moderately firm consistency, from 2 to 4 mm. in diameter, which form almost confluent plaques in some places but have a beadlike arrangement in others. In addition, the skin above the shins is atrophic and covered with fine telangiectases, and in the center of the right shin is a shallow ulcer of 1 cm. in diameter.

The complement fixation reaction of the blood was positive. Microscopic examination of one of the "waxy" papules outside the irradiated area revealed a wide band of hyperkeratosis, thickening of the granular layer to three layers and mild acanthosis in the epidermis. The predominant change in the dermis was vascular dilatation, which involved all the vessels and lymph spaces. There was slight swelling of the walls of the vessels and a scarce perivascular lymphocytic infiltrate. A section stained with methylrosaniline chloride did not reveal amyloid.

DISCUSSION

DR. W. T. GOECKERMAN: To me this is a rare and distinctive, if not classic, picture. I have seen probably half a dozen cases of this type over the years, and clinically they closely resemble each other in their appearance and behavior. I believe that they do not belong in the same category with lichen planus but are more closely related to neurodermatitis. For want of a better term I have called them "lichen ocreaformis." Possibly the coiners of this term would take issue with me. However, I maintain that these cases are of a distinctive group. I recall 2 patients that were studied intensively and whose confidence I gained. They were constantly plagued by recollection of sexual experiences of a profoundly abnormal character. I cannot help feeling that any therapy of value in these cases must be based on carefully planned psychotherapy.

DR. L. H. WINER (by invitation): I observed some of these chronic verrucous lesions to contain amyloid histologically. When it is not seen in a section that does not mean it is not there. When the section is stained with methylrosaniline chloride but Canada balsam or levulose, which is acid in reaction, is used to cover it, the bright red color is destroyed. The test of injecting congo red directly into the lesion is of more definite value. A number of cases have been presented which histologically did not show amyloid at first presentation because of the difficulty in staining.

DR. M. E. OBERMAYER: Disregarding the damage from irradiation, with which we are all in agreement, the clinical appearance of the eruption is suggestive of two diseases: localized amyloidosis and lichen ruber moniliformis. The former can be ruled out by the absence of amyloid (and I am glad of Dr. Winer's reminder as to the superiority of injections of congo red over staining the sections in determining the presence or absence of the substance). The latter diagnosis is supported by the histologic observations, which are almost identical with those in the case of Dr. Miller and Dr. Wilson recently published in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. If one examined the patient carefully one must have noticed the original eruption in the form of waxy striate papules, for which roentgen rays were administered. While this eruption is highly suggestive of lichen ruber moniliformis, I must admit that the papular form of dry neurodermatitis may at times imitate it closely. The intensive pruritus and the psychoneurotic features of the patient's personality, which did not escape my observation, are in line with such a suggestion. Yet, I favor the diagnosis under which the patient was presented.

Cheese Mite Dermatitis. Presented by DR. N. P. ANDERSON.

B. B., a white man aged 21, a food processor by profession, noticed three weeks ago the appearance of a severely pruritic eruption on the flexor surfaces of the arms and forearms which developed after the unloading of several boxes of cheese on a hot day.

He presented an eruption on the aforementioned areas which at first glance appeared to be scabies. Closer examination revealed numerous erythematous wheal-like lesions capped with a minute pinhead-sized vesicle.

Cheese mites (Tyroglyphus longior) were easily demonstrated from a sample of cheese. A slide containing the animal parasites was demonstrated.

DISCUSSION

DR. C. RUSSELL ANDERSON: This recalls an interesting case that I saw recently in a woman who had dermatitis over a scar in the region of the right breast, which had been removed because of carcinoma. She had a device made of sponge rubber to fill in the defect. She worked as a draftsman, and when she was bending over the table this false breast would rise up and make her appear lopsided. She therefore removed the sponge rubber and filled the brassiere with rice. This would drop when she bent over, and the false breast would remain in a natural position when she rose up. Three or four days later a papular dermatitis developed, which at first glance resembled carcinoma *en cuirasse*, but each papule had a punctum in the center. The rice was found to be infested with mites.

MAJOR R. L. SAUNDERS (by invitation): In grain processing centers, where all types of cereals are made, grain mites are common. The grain men call them "tumbling grain." In susceptible persons it produces a dermatitis due to Tyroglyphus farinae.

Book Reviews

Studies on Acarus Scabiei and Scabies. By Bjørn Heilesen. Acta dermatovenereologica, volume XXVI, supplement XIV. Pp. 370, with 63 illustrations. Copenhagen, Denmark: Rosenkilde and Bagger, 1946.

The investigations dealing with the scabies mite and the eruption of scabies started in 1942 at the dermatovenereological outpatient clinic of the Kommunehospital and at the University Institute of Histology and Embryology in Copenhagen, Denmark. The studies were continued in 1943 at the dermatovenereological department of St. Göran's Hospital (chief: Dr. Bo Tarras-Wahlberg), at the dermatovenereological clinic of Kungliga Karolinska Institutet (chief: Prof. Sven Hellerström), and at the entomologic department of the Natural History Museum in Stockholm. In 1945 the studies were brought to an end at the dermatovenereological Clinic of the University of Copenhagen, at the Rigshospital (chief: Prof. H. Haxthausen).

This book consists of two parts. The first part deals with a historical survey of the morphology, biology and internal anatomy of the acarus and with sensitization of the human skin to the mite. The second part deals with the author's own investigations in regard to the anatomy of egg, larva, nymph and adult mite, the internal anatomy of the mite, the developmental cycle of the acarus and the sensitivity of the skin in patients with scabies and in control persons.

There are 63 illustrations dealing with the anatomy of the mite, including diagrams and photomicrographs of the mite in the tissue and photographs of reconstruction of the burrow.

This book was written as a thesis for a doctorate and contains an enormous amount of detailed scientific work.

X-rays and Radium in the Treatment of Diseases of the Skin. By George M. MacKee, M.D., and Anthony C. Cipollaro, M.D. Contributor, Hamilton Montgomery, M.D. Fourth edition. Price, $10. Pp. 668, with 321 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1946.

The fourth edition of this textbook maintains the high standard of excellence established by its predecessors. It is a most useful product of the many years of research and experience of its two authors in the treatment of diseases of the skin with roentgen ray and radium.

In the third edition a number of collaborators contributed to and helped revise the individual chapters. This is not so in the present edition, but much of the material which was added by these collaborators has been retained. The book has been made more compact and, in the opinion of the reviewer, more readable by the elimination of some material, such as the chapter on roentgen ray spectroscopy. This subject, according to the authors, defies simplification and has a limited field of usefulness to the average dermatologist.

The arrangement of material is essentially the same as in previous editions, progressing from the historical aspects through sections devoted to physics, technic, pathology and the methods of treating individual diseases.

The chapter on the pathologic histology of radiodermatitis is contributed by Dr. Hamilton Montgomery and is enhanced by the addition of two colored plates illustrating chronic radiodermatitis and radio epidermitis. New material includes discussion of epithelitis and epidermitis, terms applied to the cutaneous and deeper reactions associated with protracted fractional treatment of either cutaneous or internal malignant lesions, according to the principles outlined by Contard.

The illustrations are excellent throughout the book. Many useful charts accompany the text, and a bibliography follows each chapter.

The book cannot be too highly recommended for use by all who treat diseases of the skin with roentgen ray and radium.